Childhood mental ability and late-onset dementia

Brian M^{c}Gurn

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Declaration

1. The research described in this thesis was the unaided work of the author, except where acknowledgement is made by reference.

2. Work I specifically did for this thesis includes case identification (chapters II and III) from case registers and clinical work. Controls for the paper in chapter II were identified by me from publicly available records held at register house in Edinburgh. Data from the Lothian birth cohort was made available for chapter III. Data from the Scottish Mental Survey 1932 was made available to me. I searched this for details on MHT score for all cases and controls used in chapter II.I designed all the databases used in preparation of this thesis and input all the data single-handedly.

3. Cognitive testing for the Lothian birth cohort was carried out by Dr. M Whiteman and Ms. Alison Pattie.

4. Statistical analyses were performed by the author under the guidance of supervisors, except the conditional logistic regression analyses in chapter II. These were performed by Dr R Lee, Statistician, Department of Epidemiology, University of Edinburgh. Professor JR Crawford gave statistical advice for the technique employed to compare regression slopes.

5. No part of this work has previously been accepted for any other degree, nor is any part of it being concurrently submitted in candidature for another degree.

Brian McGurn
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Abstract

In the many epidemiological studies of potential risk factors for dementia, lower mental ability in childhood and in early adult life have been associated with increased risk of dementia. Mechanisms underlying this association are not clear. Of great interest is the emerging evidence linking vascular risk factors to both Alzheimer's disease (AD) and vascular dementia (VaD). Studying life-course cognitive change requires a measure of cognitive ability in early life. The Scottish Mental Survey of 1932 (SMS1932) gives a valid measure of childhood mental ability age 11 years, the Moray House Test (MHT).

1. Relation of MHT to risk of dementia

Cases with vascular dementia had a lower MHT score than controls (mean MHT in cases = 34.0, mean MHT in controls 41.5, p=0.02). This translates to an odds ratio of 0.68 (95% CI 0.50 – 0.94; p=0.021) for every 10 point increase in MHT. There was no relationship demonstrated between childhood mental ability and late-onset AD. This association between childhood mental ability and vascular dementia has not been described previously.

2. Utility of estimation of pre-morbid intelligence in dementia

The estimation of pre-morbid mental ability is often required to demonstrate the cognitive decline required to diagnose dementia. The neuropsychological test most frequently used is the National Adult Reading Test (NART). A question remains about the use of the NART in dementia: some studies have shown NART scores to be lowered in dementia. NART scores were compared in cases with dementia (n=45) to healthy volunteers (n=550). Cases with dementia scored lower on the NART in old age, but also scored lower on MHT age 11. After adjusting the NART score for MHT age 11, the dementia and non-dementia groups no longer differed on NART scores. Pearson correlations between NART and MHT (measured more than 60 years apart) were similar in the dementia group (r = .60) and the non-dementia group (r = .63). These results confirm that the NART is a valid test of pre-morbid mental ability even in the presence of mild-moderate dementia.

3. Childhood mental ability and vascular risk.

Changes on the resting electrocardiograph (ECG) can be considered a marker of vascular disease. Cognitive test scores were compared in a group of people with and without ECG changes. There was no difference in MHT between the two groups. Men with left ventricular hypertrophy had lower MMSE. Both left ventricular hypertrophy and conduction defects are associated with reduced scores on verbal fluency in women. These results show that even in relatively healthy volunteers, those with markers of vascular disease have lower scores on some tests of cognitive function.

Overall, this thesis establishes that lower childhood mental ability is associated with higher risk of dementia. This occurs for vascular but not Alzheimer's dementia. These results are generally supportive of an important vascular contribution to cognitive impairment: lower childhood mental ability is associated with increased cardiovascular risk and hypertension. This is confirmed by a study showing that ECG changes are associated with lower scores on some test of cognition. Additionally, this thesis establishes that a reading test used to estimate pre-morbid mental ability remains valid even in moderate dementia. Future studies are required to examine precise roles of childhood mental ability and risk of dementia particularly the relation of vascular factors to AD and cognitive decline.

Publications arising from this thesis

McGurn B, Starr JM, Topfer J, Pattie A, Whiteman M, Lemon H, Whalley LD & Deary IJ. Pronunciation of words is preserved in dementia, validating premorbid IQ estimation. Neurology 2004; 62: 1184-1186

Starr JM, McGurn B, Whiteman M, Pattie A, Whalley LJ & Deary IJ. Life long changes in cognitive ability are associated with prescribed medications in old age. International Journal of Geriatric Psychiatry 2004; 19: 327-332

List of abbreviations used in this thesis

ABC1921	Aberdeen Birth Cohort 1921
AD	Alzheimer's disease
AMT	Abbreviated Mental Test
APOE	Apolipoprotein E
A-V	Atrio-Ventricular
BMI	Body Mass Index
BP	Blood Pressure
CAMCOG	The cognitive and self-contained part of CAMDEX
CAMDEX	Cambridge Examination for Mental Disorders of the Elderly
CAPE	Clifton Assessment Procedures for the Elderly
CERAD	Consortium to Establish a Registry for Alzheimer's Disease
CI	Confidence interval
CRT	Choice Reaction Time
CT	Computerised Tomography
CVA	Cerebro-vascular accident (stroke)
CVD	Cardiovascular disease
df	Degrees of freedom
DOB	Date of Birth
DSM	Diagnostic and Statistical Manual of Mental Disorders
ECG	Electrocardiograph
EEG	Electroencephalogram
fMRI	Functional Magnetic Resonance Imageing
GC	Grammatical Complexity

GEE	Generalised Estimated Equations
HOPE	The Healthy Old People in Edinburgh study
HR	Hazard Ratio
ICD	International Classification of Diseases
ID	Idea Density
IQ	Intelligence Quotient
LAD	Left axis deviation (an ECG abnormality)
LBBB	Left bundle-branch block (an ECG abnormality)
LBC1921	Lothian Birth Cohort 1921
LMTC	Lothian Memory Treatment Centre
LVH	Left Ventricular Hypertrophy
MCI	Mild Cognitive Impairment
MHT	Moray House Test (version number 12)
MHT-11	MHT age approximately 11
MHT-80	MHT age approximately 80
MHVS	Mill Hill Vocabulary Scale
MI	Myocardial infarction
MID	Multi-infarct dementia
MMSE	Mini-mental state examination
MRC CFAS	Medical Research Council Cognitive Function and Ageing Study
MRI	Magnetic Resonance Imageing
NART	National Adult Reading Test
NHS	National Health Service
NIA	National Institute on Aging (USA)

NINDS-ADRA	National Institute of Neurological Disorders and Stroke and the Alzheimer's Disease and Related disorders Association
NS	Non-significant (statistically)
OR	Odds ratio
PET	Positron Emission Tomography
REH	Royal Edinburgh Hospital
RPM	Raven's Progressive Matrices
RR	Relative risk
RVH	Royal Victoria Hospital
SCRE	Scottish Council for Research in Education
SD	Standard Deviation
SMS1932	Scottish Mental Survey 1932
SPMSQ	Short Portable Mental Status Questionnaire
VaD	Vascular dementia
VIQ	Verbal IQ
WAIS	Wechsler Adult Intelligence Scale
WHO	World Health Organization
χ^2	chi-squared

Chapter I: Childhood mental ability and late-onset dementia

Part 1. General introduction

Alzheimer's disease (AD) is the commonest cause of dementia. Yet, its cause or causes are not known. The classic risk factors for this disease, though, have been well described. They include increasing age (Bachman et al., 1993; Schoenberg, Kokmen & Okazaki, 1987), female sex (McGonigal et al., 1993), a positive family history (Breitner et al., 1988) and possession of the ε4 allele of the apolipoprotein E (*APOE*) gene (Myers et al., 1996; Notkola et al., 1998; Polvikoski et al., 2001). Known inherited defects account for 1-2% of cases of late-onset AD (Kehoe et al., 1992; Pericak-Vance et al., 2000). There are many other risk factors for neurodegenerative diseases including endocrine, immune and metabolic disorders (Brown et al., 2005). The precise relation of these factors to AD remains poorly categorized. Complex gene-environment interactive models have been cited as the potential likeliest causes of AD, although they currently remain vaguely described (Rao et al., 1996; Brown et al., 2005). Recently, the concept that vascular pathology might play a role in the aetiology of AD has been explored, and indeed vascular dementia (VaD) and AD share several risk factors (Bowler & Hachinski, 2003).

There is some evidence that early life factors may contribute to dementia susceptibility. However, the nature of this disease does not lend itself particularly well to the study of such putative environmental associations. Late-onset disease is defined as dementia diagnosed after the age of 65. This means that there is a very long lag period between potential exposure(s) to disease manifestation. This is further complicated by the fact that there is almost certainly a very long prodromal or pre-clinical phase that can precede the diagnosis of dementia by many years, leading to a great deal of diagnostic uncertainty.

The precise associations of environmentally-driven risk factors and cognitive decline are not known. One theory is that people have a 'cognitive reserve' (Satz, 1993; Stern, 2002) and that if people fall below a 'dementia threshold' they have enough cognitive impairment to be diagnosed with dementia. In this model, the decline on an individual's cognitive status must be viewed in the context of that individual's cognitive reserve. A major determinant of cognitive reserve is likely to be mental ability in adulthood (i.e. a pre-morbid or pre-dementia mental ability). In turn, a major correlate of adult mental ability is childhood IQ (Deary et al., 2000). This thesis will focus on childhood mental ability and its possible effect on risk of dementia and explores possible mechanisms of action especially vascular risk factors.

Aims of this thesis

This thesis aims to explore the association between childhood mental ability and late-onset dementia. Studying individual differences in cognitive ageing and cognitive decline in later life requires repeated measures of cognition. The Scottish Mental Survey of 1932 (SMS1932) gives a valid measure of childhood ability, which can then be compared to cognitive measures in later life. As this thesis hinges on this unique study, the SMS1932 and subsequent follow-up studies are described in some detail in part 2 of this introductory chapter.

The aims of this thesis are achieved by describing original research using data from the SMS1932 and its follow-up studies. Three main aims naturally split this thesis into chapters.

Firstly, I test the hypothesis that lower mental ability in childhood increases the likelihood of dementia in old age, analysing whether this is general to dementia *per se* or specific to either AD or VaD as a particular cause of dementia. Chapter I introduces the concept of childhood and early life mental ability and what role this

plays in future risk of dementia and cognitive decline, whilst chapter II describes a case-control study of childhood mental ability and late-onset dementia.

Secondly, this thesis discusses the estimation of pre-morbid intelligence, a very important tool in demonstrating the decline required to make a diagnosis of dementia. This may be considered as a methodological imperative. As will be seen in chapter III, there is a scarcity of 'true' pre-morbid mental ability measures. Childhood mental ability, measured by the MHT allows such a pre-morbid measure of mental ability. This thesis is able to assess the validity of using an estimate of pre-morbid intelligence as a diagnostic tool in dementia. This is achieved by comparing an actual measure of childhood ability (the MHT) to the test currently most used to estimate pre-morbid ability in both clinical practice and research (the National Adult Reading Test). This research is described in chapter III.

Lastly, in chapter IV, this thesis attempts to examine possible mechanisms linking childhood mental ability to late-onset dementia. To achieve this, links between cognitive function in later life, childhood mental ability and vascular risk factors are explored. In this case the electrocardiograph (ECG) is used as a marker of vascular disease.

This introductory chapter begins in part 1 with a general introduction outlining the diagnosis of dementia and its specific aetiologies. Some issues of environmental associations in dementia are explored. Of great importance is the concept of vascular factors in AD and cognitive ageing, and these are discussed at some length. As already mentioned, the SMS 1932 is vital to the methodology of this thesis and merits a detailed description in part 2 of this chapter. I finish this introduction in part 3 by going on to review literature exploring the relationship between early life mental ability and late life cognitive status.

Defining dementia

Dementia is defined by the World Health Organization (WHO) International Classification of Diseases 10th revision (ICD-10) as:

"a syndrome due to disease of the brain, usually of a chronic or progressive nature in which there is disturbance of multiple higher cortical functions, including memory, thinking, orientation, comprehension, calculation, learning capacity, language and judgement. Consciousness is not clouded. The impairments of cognitive function are commonly accompanied, and occasionally preceded by deterioration in emotional control, social behaviour, or motivation. This condition occurs in Alzheimer's disease, in cerebrovascular disease and in other conditions primarily or secondarily affecting the brain" (World Health Organisation, 1992, p. 45).

In addition, the following paragraph describes the features required to make the diagnosis of dementia.

"The primary requirement for diagnosis is evidence of a decline in both memory and thinking which is sufficient to impair personal activities of daily living.....The impairment of memory typically affects the registration, storage, and retrieval of new information, but previously learned and familiar material may also be lost, particularly in the later stages. Dementia is more than dysmnesia: there is also impairment of thinking and of reasoning capacity, and a reduction in the flow of ideas. The processing of incoming information is impaired, in that the individual finds it increasingly difficult to attend to more than one stimulus at a time, such as taking part in a conversation with several persons, and to shift the focus of attention from one topic to another. If dementia is the sole diagnosis, evidence of clear consciousness is required. However, a double diagnosis of delirium superimposed upon dementia is common. The above symptoms and impairments should have been evident for at least 6 months for a confident clinical diagnosis of dementia to be made." (World Health Organization, 1992, p. 46)

The WHO used the ICD-10 to specify some criteria that must be fulfilled in terms of application of the diagnosis for research purposes (World Health Organization, 1993). These criteria are outlined in the text box below.

Text-box 1.1: Diagnostic criteria for dementia as applicable for research purposes (adapted from World Health Organization, 1993)

Dementia: diagnostic criteria for research

G1. Evidence of each of the following:

(1) A decline in memory, which is most evident in the learning of new information, although in more severe cases, the recall of previously learned information may be also affected. The impairment applies to both verbal and nonverbal material. The decline should be objectively verified by obtaining a reliable history from an informant, supplemented, if possible, by neuropsychological tests or quantified cognitive assessments.

(2) A decline in other cognitive abilities characterized by deterioration in judgement and thinking, such as planning and organizing, and in the general processing of information. Evidence for this should be obtained when possible from interviewing an informant, supplemented, if possible, by neuropsychological tests or quantified objective assessments. Deterioration from a previously higher level of performance should be established.

The overall severity of the dementia is best expressed as the level of decline in memory or other cognitive abilities, whichever is the more severe (e.g. mild decline in memory and moderate decline in cognitive abilities indicate a dementia of moderate severity).

G2. Preserved awareness of the environment (i.e. absence of clouding of consciousness (as defined in F05, criterion A)) during a period of time long enough to enable the unequivocal demonstration of G1. When there are superimposed episodes of delirium the diagnosis of dementia should be deferred.

G3. A decline in emotional control or motivation, or a change in social behaviour, manifest as at least one of the following:

(a) emotional lability
(b) irritability
(c) apathy
(d) coarsening of social behaviour

G4. For a confident clinical diagnosis, **G1** should have been present for at least six months; if the period since the manifest onset is shorter, the diagnosis can only be tentative.

Assessment of the severity of dementia

In clinical practice, dementia is often classed as mild, moderate or severe, though often this split seems arbitrary. ICD-10 helps with classification of the severity of disease, for both severity of memory impairment and severity of impairment in other cognitive processes (World Health Organization, 1993, pp. 45-46). For memory the severity is assessed as:

Mild: a degree of memory loss sufficient to interfere with everyday activities, though not so severe as to be incompatible with independent living. The main function affected is the learning of new material. For example, the individual has difficulty in registering, storing and recalling elements in daily living, such as where belongings have been put, social arrangements, or information recently imparted by family members.

Moderate: A degree of memory loss which represents a serious handicap to independent living. Only highly learned or very familiar material is retained. New information is retained only occasionally and very briefly. The individual is unable to recall basic information about where he lives, what he has recently been doing, or the names of familiar persons.

Severe: a degree of memory loss characterized by the complete inability to retain new information. Only fragments of previously learned information remain. The subject fails to recognize even close relatives.

For decline in other cognitive abilities the severity is assessed as:

Mild. The decline in cognitive abilities causes impaired performance in daily living, but not to a degree making the individual dependent on others. More complicated daily tasks or recreational activities cannot be undertaken.

Moderate. The decline in cognitive abilities makes the individual unable to function without the assistance of another in daily living, including shopping and handling money. Within the home, only simple chores are preserved. Activities are increasingly restricted and poorly sustained.

Severe. The decline is characterized by an absence, or virtual absence, of intelligible ideation.

Dementia sub-types

Once dementia is diagnosed, it usually follows that the type of dementia is characterised. The most common type of dementia is Alzheimer's disease (AD), with the second most common type being vascular dementia (VaD).

Alzheimer's disease

ICD-10 defines AD as:

"a primary degenerative cerebral disease of unknown etiology, with characteristic neuropathological and neurochemical features. It is usually insidious in onset and develops slowly but steadily over a period of years. This period can be as short as 2 or 3 years, but can occasionally be considerably longer. The onset can be in middle adult life or even earlier (Alzheimer's disease of presenile onset), but the incidence is higher in later life (Alzheimer's disease of senile onset)..... In cases with a later onset, the course tends to be slower and to be characterized by more general impairment of higher cortical functions.....

There are characteristic changes in the brain: a marked reduction in the population of neurons, particularly in the hippocampus, substantia innominata, locus ceruleus, and temporoparietal and frontal cortex; appearance of neurofibrillary tangles made of paired helical filaments; neuritic (argentophil) plaques, which consist largely of amyloid and show a definite progression in their development (although plaques without amyloid are also known to exist); and granulovacuolar bodies. Neurochemical changes have also been found, including a marked reduction in the enzyme choline acetyltransferase, in acetylcholine itself, and in other neurotransmitters and neuromodulators.

As originally described, the clinical features are accompanied by the above brain changes. However, it now appears that the two do not always progress in parallel: one may be indisputably present with only minimal evidence of the other. Nevertheless, the clinical features of Alzheimer's disease are such that it is often possible to make a presumptive diagnosis on clinical grounds alone.

Dementia in Alzheimer's disease is at present irreversible." (World Health Organization, 1992, p. 47).

Text-box 1.2 lays out the specific criteria required to positively diagnose probable AD.

Text-box 1.2: Diagnostic guidelines for AD adapted from ICD-10 (World Health Organization, 1992, p. 48)

Diagnostic guidelines for AD

The following features are essential for a definite diagnosis:

a) Presence of a dementia as described above.

b) Insidious onset with slow deterioration. While the onset usually seems difficult to pinpoint in time, realization by others that the defects exist may come suddenly. An apparent plateau may occur in the progression.

c) Absence of clinical evidence, or findings from special investigations, to suggest that the mental state may be due to other systemic or brain disease which can induce a dementia (e.g. hypothyroidism, hypercalcaemia, vitamin B12 deficiency, niacin deficiency, neurosyphilis, normal pressure hydrocephalus, or subdural haematoma).

d) Absence of a sudden, apoplectic onset, or of neurological signs of focal damage such as hemiparesis, sensory loss, visual field defects, and incoordination occurring early in the illness (although these phenomena may be superimposed later).

Vascular Dementia

ICD-10 gives the following definition:

"Vascular (formerly arteriosclerotic) dementia, which includes multi-infarct dementia, is distinguished from dementia in Alzheimer's disease by its history of onset, clinical features, and subsequent course. Typically, there is a history of transient ischaemic attacks with brief impairment of consciousness, fleeting pareses, or visual loss. The dementia may also follow a succession of acute cerebrovascular accidents or, less commonly, a single major stroke. Some impairment of memory and thinking then becomes apparent. Onset, which is usually in later life, can be abrupt, following one particular ischaemic episode, or there may be more gradual emergence. The dementia is usually the result of infarction of the brain due to vascular diseases, including hypertensive cerebrovascular disease. The infarcts are usually small but cumulative in their effect." (World Health Organization, 1992, p. 50).

The guidelines for making the diagnosis are laid out in text-box 1.3.

Text-box 1.3: Diagnostic guidelines for VaD adpted from ICD-10 (World Health Organization, 1992, p. 50)

Diagnostic guidelines for VaD

a) The diagnosis presupposes the presence of a dementia as described above.

b) Impairment of cognitive function is commonly uneven, so that there may be memory loss, intellectual impairment, and focal neurological signs.

c) Insight and judgement may be relatively well preserved.

d) Personality is believed to be relatively well preserved, but personality changes may be evident in a proportion of cases with apathy, disinhibition, or accentuation of previous traits such as egocentricity, paranoid attitudes, or irritability.

e) An abrupt onset or a stepwise deterioration, as well as the presence of focal neurological signs and symptoms, increases the probability of the diagnosis; in some cases, confirmation can be provided only by computerized axial tomography or, ultimately, neuropathological examination.

f) Associated features are:
   - hypertension
   - carotid bruit
   - emotional lability with transient depressive mood, weeping or explosive laughter
   - transient episodes of clouded consciousness or delirium, often provoked by further infarction

Diagnosing dementia: difficulties, uncertainties and overlap

There is no diagnostic category for mixed dementia in ICD-10. This presents a problem. ICD-10 itself says:

"In a certain proportion of cases, the features of Alzheimer's disease and vascular dementia may both be present. In such cases, double diagnosis (and coding) should be made. When the vascular dementia precedes the Alzheimer's disease, it may be impossible to diagnose the latter on clinical grounds." (World Health Organization, 1992, p. 48).

On the same page of ICD-10, this message is repeated:

"Dementia in Alzheimer's disease may coexist with vascular dementia.....as when cerebrovascular episodes (multi-infarct phenomena) are superimposed on a clinical picture and history suggesting Alzheimer's disease. Such episodes may result in sudden exacerbations of the manifestations of dementia. According to postmortem findings, both types may coexist in as many as 10-15% of all dementia cases." (World Health Organization, 1992, p. 48).

The application of precise diagnostic criteria in research into dementia is of vital importance. Firstly, it allows some certainty of diagnosis when discussing dementia between different research studies. A flaw of many studies is that they may over- or under-represent certain types of dementia. Secondly, it allows research findings for subjects with a particular type of dementia of a defined level of severity to be generalised to the population of people with that dementia type and severity. However, as will be seen below, level of diagnostic accuracy varies depending on the particular diagnostic criteria used (Erkinjuntti et al., 1997), potentially leading to a great deal of uncertainty. Similarly, levels of severity (as defined above) are vague and rather arbitrary.

The important features for making the diagnosis of dementia and sub-type were highlighted above in text-boxes 1.1, 1.2 and 1.3. However, a closer analysis of these texts begins to reveal some diagnostic uncertainty. For example, in text-box 1.1, supporting evidence for 'dementia' would be a decline or change in social behaviour, specifically mentioning emotional lability, apathy and irritability. Yet, these are defined as associated features of VaD (text-box 1.2), which instantly makes the

diagnosis of AD much less likely and more difficult to make. Similarly, in text-box 1.3, the presence of super-imposed delirium might be taken to imply that VaD is the more likely diagnosis. However, people with AD often present with delirium that is not due to stroke or VaD. Hypertension is defined as an associated feature of VaD but is also a risk factor for the development of AD (Launer et al., 2000; Petrovich et al., 2000; Kivipelto et al., 2001).

Practically speaking, the major difficulty is not usually in making a diagnosis of dementia, although this may be difficult in the very early stages. Rather, it is in determining which type of dementia is present. This is true of clinical practice but is certainly of major importance in research into dementia, AD and VaD. Making the diagnosis of sub-type of dementia is notoriously difficult in life. The gold-standard diagnosis of AD is pathological. Any diagnosis of AD made in life is presumptive, and is largely a diagnosis of exclusion. Ultimately it may be impossible to differentiate sub-types of dementia based on clinical features alone.

Clearly, there is much overlap between AD and VaD. The point of demonstrating the difficulty in separating AD and VaD is that this in itself may reflect inherent similarities between these two – currently mutually exclusive – types of dementia. This is crucial to take into account in the research of causes of and risk factors for AD and dementia.

Environmental factors and dementia

This short section should possibly be prefaced by the following phrase: the precise biological determinants of cognitive ageing remain unknown. There is a vast heterogeneity underlying the biomedical and behavioural factors that may influence cognitive function and the presentation of dementia (Cohen-Mansfield, 2000). These factors, which may have a varying impact at different stages in life, might best be demonstrated as a table (table 1.1).

Table 1.1: proposed factors that may influence late life cognition and presentation of dementia

	Point in life at which factor exerts influence		
	early	**throughout life**	**late**
Biomedical	genetic predisposition gender	physical health brain trauma	genetic predisposition neurological damage (especially stroke) acute physical illness
Psychosocial		stress personality (motivation)	affect social support network
Environmental	socio-economic education	education lifestyle (smoking, alcohol) employment	stimulation level

As already mentioned, it is very difficult to state with any certainty at which point in a person's life any of these factors operate. For example, more years spent in education may protect against cognitive decline. Whether this begins very early in life or exerts its effect in very late-life is not clear.

Loosely, environmental factors have long been thought to be associated with dementia. In literature discussing the aetiology of AD mention is often made of the genetic and environmental risk factors, though precise details for these 'environmental factors' are often scant. In recent years there has been interest in the role of free radicals and oxidative stress in neurodegeneration and neuronal cell death (Smith et al., 1995; Moreira et al., 2005). There is some evidence that inflammation, both systemic and brain-related, is associated with AD (Wilson et al., 2002). The acute phase protein CRP has been demonstrated in increased concentration in people with dementia (Schmidt et al., 2002). Exact pathological mechanisms linking 'inflammation' to AD remain unclear, though it has been suggested that atherosclerosis may be involved along the way (Hackam & Annand, 2003), as have a variety of cytokine responses and cytokine dysregulation (Wilson et al., 2002).

The subject of environmental factors and dementia has been raised in this section to introduce the concept that there are extrinsic factors important in the causation, promotion or clinical manifestation of dementia. These extrinsic factors have often been labelled as 'environmental'.

A list of risk factors for AD as reported in epidemiological literature is shown in table 1.2.

Table 1.2: A list of risk factors for AD as reported in epidemiological literature

ageing	migraine
atherosclerosis	depression
stroke/TIA	dietary fat intake
diabetes	thrombogenic factors
smoking	apolipoprotein ε4
hyperlipidaemia	hyperhomocysteinaemia
coronary artery disease	head injury
hypertension	lower mental ability in childhood
hypotension	fewer years of education
atrial fibrillation	

Out of these many risk factors, possibly of greatest interest is the emerging body of evidence linking vascular factors and AD. Analysis of the risk factors in table 1.2 shows that many indeed can be considered 'vascular' in nature. Although vascular factors may be described as 'environmental', it is equally important to consider that there may be an important genetic component in vascular cognitive impairment (Leblanc et al., 2006).

A limitation of this thesis is that it concentrates on vascular risks; there are many putative causal factors which could also be studied and have equal credence in the theories of the causes of AD and dementia. More work is required to clarify the role

of vascular factors in AD and where these vascular factors sit in relation to other plausible environmental factors.

Vascular factors, dementia and cognitive impairment

Table 1.2 above detailed the many vascular risk factors for dementia and AD. For this reason, vascular factors in dementia receive detailed discussion in the following section of this thesis. Part of the rationale behind this lengthy discussion at this point is that the mechanism of how low mental ability in early life acts as a risk factor for dementia is not known. Childhood mental ability and years of education have been described as 'environmental' risk factors associated with dementia. It must be considered that low childhood mental ability is itself a vascular risk factor or at least has a major association with vascular risk.

AD is a neurodegenerative dementing disorder of unknown cause. VaD is a dementing disorder of many aetiological starting points, with causal vascular associations, but a final common pathway. The presence of vascular brain lesions by definition instantly excludes a diagnosis of AD (NINCDS-ADRA, DSM-IV & ICD-10 criteria). Yet, autopsy studies have shown that the two conditions are frequently found in the same brain of a person with dementia (MRC CFAS, 2001; Snowdon et al., 1997). This could reflect two common disparate pathological processes linked by chance. More likely, though, is that the two have a shared underlying cause, or at the very least, the presence of one pathology modifies the clinical expression of the other and vice versa.

The splitting of dementia into distinct disorders following a report in 1955 (Roth, 1955) may have paradoxically held back the study of the causes of AD in that it has excluded the possibility of a vascular contribution to AD pathology (Breteler et al., 1994; Stewart, 1998), causing a "stumbling block in the clinical management and in the search for a cure of AD" (de la Torre, 2002, p. 1152).

Alois Alzheimer set out to investigate 'arteriosclerotic brain degeneration'. His discovery of neuritic amyloid plaques and neurofibrillary tangles was of profound scientific importance, but did not immediately change the way that dementia was viewed. As recently as the 1960's arteriosclerosis was believed to be the commonest cause of dementia, with AD thought to be a rare condition. A medline search of papers published in 1975 including "Alzheimer" as a keyword revealed that only 42 papers were published that year (Boller & Forbes, 1998). The first edition of the DSM published in 1952 (American Psychiatric Association, 1952) did not mention Alzheimer's disease by name, but rather referred to "organic brain syndrome" (Boller & Forbes, 1998).

It was only upon the discovery in large autopsy series that Alzheimer's pathology was almost ubiquitous that AD became recognised as the commonest cause of dementia. The fact that vascular changes are also ubiquitous seems to have been overlooked until recently. The possibility that Alzheimer's disease pathology and vascular pathology may be linked has not been a major focus of research to date, but is beginning to gain prominence (Kivipelto & Solomon, 2006).

Traditionally, vascular dementia is thought to make up 25-30% of all cases of dementia (O'Brien et al., 2003; Skoog et al., 1993). This figure can vary depending on criteria used for diagnosis and population studied and has been reported as accounting for between 9% and 50% of dementias (Bowler & Hachinski, 2003a). The prevalence of VaD is also variable depending on whether so-called 'mixed' dementia is classed as vascular or otherwise. Rocca & Knopman (2003) conclude "It remains difficult to draw conclusions about the frequency and distribution of VaD. The data from current studies cannot be compared and reconciled easily. Disagreement on diagnostic criteria and their field implementation remains the major problem." The epidemiology of VaD is not therefore as well defined as that for AD, the important point being that the major problem is the lack of consistent internationally accepted diagnostic criteria for diagnosing and monitoring the disease. In any case, attempting to split the dementias into VaD and AD and

describing their separate epidemiology may be divisive and once again limit the study of factors common to both.

There is growing evidence that vascular dementia is not only caused by the traditional multi-infarct model (Hachinski, Lassen & Marshall, 1974) but that several vascular pathologies can lead to dementia (Esiri, Wilcock & Morris, 1997; Pohjasvaara et al., 2000). In an attempt to clarify current concepts of 'vascular dementia' the International Psychogeriatric association convened a special meeting, which suggested a terminology to fit in with the changing classification of vascular cognitive impairment. Adapted from O'Brien et al. (2003) this is shown as table 1.3.

Table 1.3: Classification and causes of sporadic vascular cognitive impairment

Post Stroke dementia
Vascular Dementia
Multi-infarct dementia (cortical vascular dementia)
Subcortical ischaemic vascular dementia
Strategic-infarct dementia
Hypoperfusion dementia
Haemorrhagic dementia
Mixed AD and vascular dementia
Vascular mild cognitive impairment

This table illustrates that there is no single vascular cause for dementia. Indeed, as will be seen when discussing pathological studies of VaD and AD, the traditionally espoused diagnosis of multi-infarct dementia is very rare (Heyman et al., 1998; Nolan et al., 1998). Table 1.3 could also imply that vascular factors impact on cognitive impairment by exerting a variety of different mechanisms.

Vascular disease is extremely common yet has a multifarious definition and pathophysiology. 'Vascular' may be interpreted loosely to include for example diseases traditionally thought of as vascular i.e. stroke disease, ischaemic heart disease, as well as risk factors with strong association with these diseases including hyperlipidaemia, hypertension, diabetes etc. However, newer ideas like increased blood-brain-barrier permeability must also be considered: the causes of dementia and age-associated cognitive decline are not yet fully understood. This part of the thesis explores the literature suggesting that vascular factors contribute to dementia, and that AD has a major vascular contribution. The role of vascular factors and cognitive decline as seen in 'normal' ageing will also be briefly explored.

Alzheimer's disease as a vasculopathic complex

JC de la Torre (2002) has laid out the following qualities for evidence that would define AD as a 'vasculopathic complex':

1. Epidemiological evidence linking vascular factors to cerebrovascular pathology that can set in motion metabolic, neurodegenerative and cognitive changes in Alzheimer brains
2. Evidence that AD and VaD share similar risk factors
3. Evidence that therapy that improves cerebrovascular insufficiency also improves AD symptoms
4. Evidence that preclinical or prodromal AD detection is possible from direct or indirect regional cerebral perfusion measurements
5. Evidence that AD clinical symptoms arise from cerebromicrovascular pathology
6. Evidence of matching clinical symptomatology in AD and VaD

7. Evidence showing overlap of cerebrovascular and neurodegenerative pathology in AD an VaD
8. Evidence that cerebral hypoperfusion can trigger hypometabolic, cognitive and degenerative changes
9. Evidence that AD is a heterogeneous and multifactorial disorder due to a variety of vascular risk factors or indicators of vascular disease

This comprehensive list is largely appropriate. However, it can perhaps be criticized for attempting to fit current evidence to a list of criteria thus validating the constructed criteria. I will refer back to some of these criteria when reviewing the literature, in the process establishing the link between vascular factors and cognitive decline.

An attempt to systematically review the field of literature of vascular risk factors and risk of dementia or cognitive decline. lies beyond this thesis; there are already many good reviews of epidemiological risk factors and AD (Breteler, 2000a; Breteler, 2000b; O'Brien et al., 2003; Bowler & Hachinski, 2003; Hachinski & Munoz, 2000; Launer, 2002; O'Brien, 2006). This is perhaps a flaw in that I have not gone into specific details of all available literature, and have not mentioned some large studies. Rather, I will describe some important and relevant literature that is illustrative of the now accepted link between vascular disease and cognitive impairment.

Vascular dementia versus Alzheimer's disease: diagnostic criteria

Before going further it is useful to look at whether current diagnostic criteria have the ability to differentiate between these two common types of dementia. This has important clinical and research methodological connotations. Possibly the most important feature has already been mentioned: the presence of cerebrovascular

disease instantly excludes the diagnosis of AD. Kudo et al. (2000) state that such firm exclusion is probably necessary for the successful prosecution of any epidemiological study. However, the result is that any vascular contribution to AD is by definition under-estimated.

Erkinjuntti et al. (1997) looked at the variability of the diagnosis of dementia depending on which criteria are applied. They examined 1879 people who took part in the Canadian study of Health and Ageing. Each participant was clinically examined and underwent neuropsychological evaluation, as well as a clinical consensus for the presence of dementia. Different diagnostic classifications were applied to the data and prevalence of dementia was found to vary dramatically depending on which diagnostic criteria were used. Overall, 3.1% of people were said to have dementia when ICD-10 criteria were used, whereas 13.7% of people were demented according to DSM-IV criteria, this figure rising to 29.1% when DSM-III were applied. This is not the only study to discover such a discrepancy. Other investigators have shown similar results, with ICD-10 criteria identifying fewer cases of dementia than DSM-IV (Henderson et al., 1994). Pohjasvaara et al. (2000) reported similar discrepancies for vascular dementia. Although primarily of concern to those attempting to compare research findings, the results must also raise a concern as to the clinical utility of detecting dementia per se let alone identifying its various sub-types. Bowler & Hachinski (2003a, p. 7) lament that "the only operational criteria available.....were developed with a view to epidemiological convenience rather than to clinical accuracy.....and the reader is encouraged to review them critically and use them cautiously". It is impossible to disagree with this conclusion. An alternative reading of the lack of concordance between various diagnostic criteria is that the two diseases, AD and VaD, have similar clinical, pathological and neuropsychological features. It may be precisely this similarity that can make AD and VaD very difficult to distinguish as separate disease entities.

Epidemiological evidence linking vascular factors to cognitive decline

There is a growing wealth of strong epidemiological evidence linking cognitive decline to vascular factors.

I will use as an example the Rotterdam study, as it represents perhaps the most important epidemiological study of vascular factors and AD (Breteler, 2000a; Breteler et al., 1994). This is a prospective, population based study aiming to "investigate determinants of chronic and disabling cardiovascular, neurodegenerative, locomotor and ophthalmological diseases" (Breteler et al., 1994, p. 1604). It began in 1990 and studied 7,983 subjects from an eligible 10,275 people age 55 or over living in a suburb of Rotterdam. Subjects included people living in institutional care. The study began with base-line assessment including medical history and several non-invasive measures of vascular disease. Dementia was identified as one of the key outcomes, and this was specifically screened for at base-line by using the MMSE and CAMDEX (Roth et al., 1986). Where there was any suspicion of cognitive impairment the subjects were subsequently examined by a neurologist and a clinical neuropsychologist to make the diagnosis of dementia. The Rotterdam study has revisited its subjects in two further waves in 1993-1994 and 1997-1999.

The Rotterdam study looked at cardiovascular disease and the distribution of cognitive function in its cohort at base-line. Cognitive test data were available for 4,971 people at base-line. After standardising for years of education, age and gender using multiple logistic regression analysis, this study showed that MMSE scores were reduced in those people with a previous CVA (mean 26.5) compared to those without (mean 27.4). The MMSE was also lower in people with peripheral arterial disease, as measured by the ratio of ankle to brachial systolic blood pressure, (mean 26.8 in those with disease compared to mean 27.6 in those without) and was lower in those with carotid artery atherosclerotic disease (mean 27.3 in those with, mean 27.7

in those without. In addition, the presence of vascular disease shifted the distribution of MMSE scores such that there were a higher proportion of people scoring below a cut-off point of 24 on MMSE in those with vascular disease. These changes in MMSE are very small and are of doubtful clinical significance. The authors argued, however, that the shift in distribution of cognitive function towards lower levels would represent an important effect in population terms. The authors concluded that "atherosclerotic disease can account for considerable cognitive impairment" (Breteler at al., 1994, p. 1608).

Subsequent investigations on the Rotterdam Study population allowed the investigators to examine specific vascular risk factors and the risk of AD. They compared 284 people with incident dementia to 1698 without. They discovered that people with atherosclerosis were more likely to develop AD (OR=3.0, 95% CI 1.5-6.0) than those without and that the risk of AD increased with severity of atherosclerosis (Hofman et al., 1997). This same paper presented data suggesting that there was a synergistic interaction between atherosclerotic disease and the *APOE* ε4 allele: those with severe atherosclerosis and at least one *APOE* ε4 allele were 20 times more likely to develop AD.

Other vascular factors which the Rotterdam investigators have found to be risk factors for AD include smoking (Ott et al., 1998), high dietary intake of fat (Kalmijn et al., 1999) and hypercoagulability including factor V Leiden deficiency (Bots et al., 1998). Diabetes mellitus was examined cross-sectionally and prospectively.

A single study, no matter how well designed, will not prove a causal link between a risk factor and a disease. It is important then to note that the findings of the Rotterdam study are replicated by many major, population-based epidemiological studies. Of particular note are the Cardiovascular Health Study (Fried et al., 1991), the Kungsholmen Project (Fratiglioni et al., 1992) and the Caerphilly Cohort (Elwood et al., 2002). A list of epidemiological risk factors for AD was shown above in table 1.2. Clearly many of these have an underlying vascular nature, illustrating

the strength of epidemiological evidence suggesting an important vascular contribution to AD.

The link between vascular disease and AD may be further clarified by examining an alternative hypothesis; namely, is AD a risk factor for vascular disease? If this were true, it may point towards a link in pathogenesis. Gale et al. (1996) examined 921 people from 5 areas of the UK who were age 65 or over. They used a very simple measure of cognitive function, the Hodkinson Abbreviated Mental Test (AMT; Hodkinson, 1972) and showed that poorer function on this test (a score of less than 8 out of 10) was associated with an increase in mortality from ischaemic stroke (RR=3.3, 95% CI 1.7-6.2). This study may be criticised for not showing an excess risk of stroke but for showing excess risk of mortality from stroke, and the test of cognition is not a sophisticated tool for assessing cognition but rather is a crude screening tool for possible impaired cognition. Ferrucci et al. (1996) published another paper looking at this link. They studied 5024 subjects who were free of stroke disease who had a mean age of 78.5. This sample came from three areas of the USA in a prospective longitudinal study. Cognition was assessed annually at interview applying Pfeiffer's Short Portable Mental Status Questionnaire (SPMSQ; Pfeiffer, 1975) and the group was split into normal, moderate impairment and severe impairment on the basis of this score. The outcome used was first incident stroke, ascertained from hospital records and death certificates. An increase in stroke incidence was demonstrated in those with cognitive impairment (RR=2.6, 95% CI 1.4-4.5 for those in lowest scoring group). Again this study may be criticised for using a crude test of cognition. However, they were also able to demonstrate that it was decline in score that was important: those who had a stable score over three years had the same risk of stroke regardless of SPMSQ score at base-line. This may be interpreted as dementia or cognitive decline rather than AD being associated with stroke. Zhu et al. (2000) investigated the relation of cognitive function to stroke incidence in a population based cohort age 75 years or over. A total of 1551 subjects with a mean age of 82.0 years were followed up for 3 years. Cognitive function was assessed by the MMSE and the outcome was incident stroke as measured by an

inpatient register. Cox proportional hazard regression analysis, adjusting for age, sex, gender and education showed that those impaired on the MMSE were more likely to have a stroke than those with normal cognition. There seemed to be a dose-dependent response: the lower the MMSE, the higher the risk.

These three studies do seem to show that poor cognition is associated with stroke, thus proving a further link between vascular disease and impaired cognition. However, the cognitive assessment used in each case was crude. Although each of the authors controlled for age, gender and education, none took into account actual premorbid (in this case pre-stroke) intelligence. It may be that the increased risk of stroke is a reflection of reduced underlying mental ability, which as discussed before is a risk factor for vascular disease and for cognitive impairment and dementia. These studies also were unable to use neuroimaging or population based health records; hence they can only comment on the most severe of strokes, those admitted to hospital. These data may be interpreted as poor cognition being a risk factor for stroke, or more likely that the cognitive impairment reflects previously unrecognised cerebrovascular disease. Further studies would be required to see if poor cognition is a risk factor for silent brain infarct or for mild stroke not requiring hospitalisation.

Can AD and VaD be distinguished clinically?

Evidence that there are clinical features unique to either AD or VaD would be indicative of discrete clinical entities. On the other hand, an inability to distinguish the two disorders clinically could imply that the two diseases may be linked, though as discussed elsewhere this need not be a causal link.

Distinguishing AD from VaD on clinical grounds remains notoriously difficult. They can present with similar symptoms. In addition, the step-wise deterioration often thought of as a standard course of multi-infarct dementia has been described in AD,

whilst a steady decline in cognitive function can be seen in VaD (Fischer et al., 1990; Skoog et al., 1993). There are no biomarkers specific to either cause of dementia. Clearly, vascular disease, vascular dementia and AD frequently co-exist in the elderly; this is exemplified by autopsy studies, and is discussed in more detail later in this chapter.

The differentiation of AD and VaD may be possible with in-depth neuropsychological assessment. Reviewing such literature begins from a fraught tautological stand-point: if one is looking at the 'typical' picture of a patient with 'vascular dementia' it will by definition have excluded anyone with AD and therefore selection bias will play a large part in the results of the neuropsychological tests. Similarly, tests which are said not to be able to differentiate the two conditions are discarded (or results not published) thus making it seem as though the differentiation is real. Studies have been aimed at proving there is a difference between VaD and AD.

Sachdev & Looi (2003) looked at the published literature on neuropsychological differentiation of AD and VaD. Although not a meta-analysis, they systematically reviewed 50 studies in this field, rejecting 18 because of methodological problems. Important problems in the published literature were difficulties with matching controls on age, sex, education and dementia severity. Case definition was also problematical. Perhaps the one major flaw is the diversity of neuropsychological tests used in these various papers. A pragmatic approach is to focus on cognitive 'domains' assessed by various tests, though this does not sit well with a neuropsychological or psychometric approach to cognitive function.

Sachdev & Looi point out that a neuroanatomical approach might predict definitive profiles for these diseases. For example temporal lobe lesions affecting cholinergic pathways lead to predominate memory problems in AD, versus the more diffuse cognitive profile seen in VaD, as the lesions involve more than one particular anatomical area. Similarly, this may explain the over-expression of 'frontal lobe'

syndrome in people with vascular insults in the frontal lobes. However, they state that in practice these differences often overlap for previously mentioned reasons including the common-place nature of co-pathology and the heterogeneity of Alzheimer's pathology. In addition, tests of cognition tend not to be sampled from a single discrete brain area and there is an inter-correlation of cognitive tests.

Not surprisingly, Sachdev & Looi (2003) concluded that for each broad area of cognition tested (including intelligence, language, attention, verbal learning and memory, non-verbal memory, conceptual function, frontal executive function and working memory) the results often conflicted with some showing that people with AD performed better than those with VaD, others showing the converse and others still showing no difference. They concluded that people with VaD tend to have poorer executive function than people with AD. They also said that the two groups do not differ in test of language or attention and that there were insufficient data to draw conclusion on differences in general intelligence.

These conclusions may be interpreted in several ways. It may be difficult to draw firm conclusions because of methodological flaws in studies: in other words, perhaps if a study employing better neuropsychological tests was better designed, then the differences would become apparent. An alternative view is that the neuropsychological tests do not show a difference because there is no difference. If the diseases shared a similar pathogenesis then this latter viewpoint would be considered more accurate.

A more recent review of vascular cognitive impairment (O'Brien, 2006) once again highlighted that the 'typical' cognitive deficits in this tend to be speed of information processing, attention and executive dysfunction (Desmond, 2004; Roman et al., 1999). O'Brien (2006) points out that the variability in cognitive presentation in dementia of Alzheimer and vascular type gives a practical difficulty as the classic screening tools (e.g. MMSE, ADAS-Cog) were developed for detecting memory deficits more associated with AD. This has led to the "positive development"

(O'Brien, 2006, p. 729) of incorporating tests of executive function (e.g. verbal fluency) into a 'bed-side' format of the VADAS-Cog (Mohs et al., 1997). This represents a pragmatic approach to aid the diagnosis of VaD versus AD but may also be using tests which deliberately 'split' the dementias neuropsychologically and once again minimising the vascular links to AD.

It is almost self-evident to state that diseases of different aetiologies will have different prognoses. If survival following the diagnosis of dementia was different in those with AD compared to those with VaD, this might imply that they are discrete entities. Aevarsson, Svanborg & Skoog (1998) looked at the survival rates in people age over 85 years in relation to AD and VaD. They discovered that after taking into account severity of dementia, there was a reduced survival rate in people with VaD compared to AD. Other investigators find similar results. Mölsa et al. (1995) looked at the survival rates for people with VaD compared to AD in a study following patients for 14 years. The relative risk of death was 3.5 (95%CI 2.4-5.1) for people with VaD, and 2.8 (95% CI 2.1-3.6) for people with AD. These results conflict with other studies which have found that survival rates are very similar regardless of dementia. (Martin et al., 1987; Heir et al., 1989; Rossler et al., 1995). Thus, the survival data are inconclusive. This might have been predicted again by the fact that differing samples (greater or lesser number of people with vascular disease) and applying different diagnostic criteria will affect the outcome. Although the data are inconclusive, people with AD might be expected to survive longer. Effectively they have had underlying vascular disease (myocardial infarction or ischaemic stroke) excluded and thus it is people with a larger burden of vascular disease who have the shorter survival (Østbyte et al., 1999). The published survival data do not then rule out an important vascular contribution to AD or age related cognitive decline.

Other investigators have looked at patterns of cognitive decline to assess if VaD and AD can be differentiated. Three of the important features traditionally associated with VaD have been abrupt onset of symptoms, a stepwise deterioration and a fluctuating course. The converse, which is an insidious onset with a progressive

decline, is thought to herald AD. Fischer et al. (1990) studied the pattern of cognitive decline in people with MID and AD. As expected, the majority (94%) of patients with AD had an insidious onset, and 81% had a steady decline. This contrasted with the MID group where 51% had an insidious onset and 50% had a gradual decline. Overall only 34% of patients labelled with MID had the characteristic features. This may be interpreted as naivety of the concept of 'multi-infarct dementia' as being relatively unrepresentative of VaD. Alternatively, it is perhaps more true to suggest that the clinical courses of these two diseases are difficult to tell apart because of similarities in the aetiology and pathophysiology of these artificially differentiated diseases.

AD and VaD: a shared vascular pathology?

Autopsy studies are of great importance in clarifying the vascular factors in dementia. The population sampled in such studies is of great importance: autopsy data on AD has tended to come from patients recruited from specialised memory clinics, leading to a major under-representation of vascular disease in the studied populations (Bowler et al., 1998). Representative community-based studies are required to illustrate the true relationship between vascular lesions, AD and cognitive decline.

Apart from showing the distribution of Alzheimer's and vascular pathologies in the population, the answers to several questions should help to determine whether AD has a significant vascular component in its aetiology:

1. Do brains of people with dementia have more vascular lesions than those without?
2. Do brains of people with Alzheimer's disease have more vascular lesions than those without?

3. Does the presence of vascular lesions correlate with cognitive impairment?
4. To what extent is AD pathology 'mixed' with vascular pathology?
5. Is there evidence of interaction between vascular lesions and AD pathology?

The widespread concomitant occurrence of both vascular and Alzheimer's pathology is well established (Gearing et al., 1995; Victoroff et al., 1995). The Neuropathology Group of the Medical Research Council Cognitive Function and Ageing Study (MRC CFAS, 1998) published the results from a large, multicentre community-based neuropathology study (MRC CFAS, 2001) looking at brain changes in relation to prospectively gathered cognitive data. This study took in 5 centres in England and Wales. Of those who had taken part in the prospective follow up of cognitive function, between 20-55% of people per centre agreed to have their brains examined by necropsy at their death. This represented 209 individuals for whom the dementia status was known. The age at death ranged from 70-103 years. Approximately 48% of these people had an ante-mortem diagnosis of dementia. In this study, even in people who had no evidence of dementia, only 13% had a normal brain. There were numerous plaques and tangles, abundant enough to warrant a diagnosis of AD in 19% and insufficient to make this diagnosis in 28%. About one-third of all the non-demented individuals had moderate or severe neuritic plaque scores. This contrasts with the finding that 36% of those who had dementia had very low or no plaque scores. This study was able to show that for the whole group, ischaemic brain lesions were also very common, being present in 78% of individuals. A multivariate logistic regression analysis suggested that low brain weight ($p = 0.04$), severe neocortical neuritic plaques ($p = 0.03$), multiple vascular diseases ($p = 0.05$) and severe amyloid angiopathy ($p < 0.001$) were the most important determinants of dementia.

The MRC CFAS is an important study. It establishes the lack of correlation between dementia and the presence of Alzheimer's pathology. It also establishes the high prevalence of ischaemic brain lesions. A limitation of this study is that it did not

allow detailed clinical investigation of all the individuals. The information available was not enough to sub-type the dementias, and thus data are not available for the associations of the various brain lesions in people with clinically diagnosed AD compared to VaD. The MRC CFAS authors suggest that this may allow us to draw conclusions about the nature of dementia as it really exists in the population. In this respect, the results are interpreted as being at odds with previous results (which were predominately drawn from highly selected, younger people). They also propose that models of the causation of dementia in the elderly need to be re-considered to include vascular or ischaemic insult.

The Consortium to Establish a Registry for Alzheimer's Disease (CERAD) collaborators published a study aiming to specifically look at the relation between cerebral infarction and clinical and neuropsychological factors in people with autopsy proven AD (Heyman et al., 1998). They enrolled 106 people with probable or possible AD (diagnosed clinically according to NINDS-ADRDA criteria) who agreed to have an autopsy on their death. This entire group had AD confirmed pathologically, having met the criteria for abundant neocortical plaques. There was evidence of AD as the sole pathology in 74 (70%). The remaining 32 cases had evidence of AD combined with vascular lesions, either infarcts, lacunar infarcts or diffuse microinfarcts. It is interesting that only 5 of these 32 people had a clinical history of stroke, which is consistent with recent data published suggesting that silent strokes may account for a significant amount of cognitive decline (Vermeer et al., 2003). The people in the CERAD study with AD plus vascular lesions tended to be older than those with AD alone. There were no significant gender differences between the groups and nor was there a difference in numbers of years of education. Hypertension seemed to be an important factor associated with cerebral infarcts, this being present in 16.2% of those with AD alone compared to 15.6 % of those with additional infarcts ($p = 0.001$). In the CERAD study, cognition was measured annually, and the results reported in this paper were for the assessment closest to the subjects' death. In terms of the effect on cognitive function, those with brain infarct had a lower median MMSE (5.5 versus 10.5, $p = 0.001$) and a lower median verbal

fluency (2 versus 3, $p = 0.042$). These results were after adjusting for age and education. There was no difference in the Boston Naming Test, Word List Learning, Word List Recall, Word List Recognition or Constructional Praxis. The authors relate the lack of a difference between the groups to a floor effect on these cognitive tests.

Some of the most compelling evidence of the interaction between vascular and Alzheimer's pathology comes from the Nun Study (Snowdon et al., 1997). This study was is one of the most important studies of cognitive ageing and will be discussed again later in part 3 of this introductory chapter in relation to early life mental ability and risk of dementia in later life. Part of the elegance of the Nun study is that all of the participating nuns gave permission for the post-mortem examination of their brains (Snowdon et al., 1996). Snowdon et al. (1997) hypothesised that the reason that many individuals with abundant Alzheimer's brain pathology did not become demented (Katzman et al., 1988b; Crystal et al., 1988) was because of an interaction between co-existing brain pathology. The subjects for this study were 102 of the nuns who had all achieved a college degree and who had died during the follow-up of this study up to 1995. The brains were examined by a neuropathologist who was blind to the cognitive status of the subjects. Scores were created for presence of Alzheimer's lesions and for the presence of vascular lesions. Alzheimer's lesions were present in sufficient numbers to make a neuropathological diagnosis of AD in 61 people. Of this group, those with brain infarcts had a significantly lower MMSE (mean=17 in AD alone, mean=8 in AD plus infarct, $p < 0.001$). A similar impairment in cognition was present for all of the cognitive tests used in the Nun Study. The prevalence of dementia in this group – who all met neuropathological diagnostic criteria for AD – was 88% for those who had brain infarcts versus 57% for those with AD lesions alone. In the group without neuropathological changes of AD ($n = 41$) there was no significant differences in mean MMSE scores and the prevalence of dementia was similar in the two groups. In only 1 of 8 cognitive tests, that of Constructional Praxis, was brain infarct associated with poorer test performance.

In order to attempt to quantify the relation between brain infarcts and cognitive function, Snowdon et al. (1997) firstly showed that there was a correlation between neurofibrillary tangles and MMSE. For each additional point in the neuropathology score, there was a 0.8 decrease in MMSE for those without infarcts and a 3.0 decrease for those with infarcts. They then went on to show that for those people with dementia who did not have brain infarcts, there were significantly greater numbers of Alzheimer's lesions in their brains. Another of the main findings in this study was that there appeared to be no relation of brain infarcts to *APOE* ε4 allele.

More work from the Nun Study has shown the lack of correlation between pathological findings and cognitive status. Riley et al. (2002) performed a study that aimed to look at pathological correlates of the full spectrum of cognitive states seen in the study population, including those people with mild cognitive impairment. There was a correlation of 0.57 between Braak staging and a 6-level rating of clinical status. However, approximately 50% of people with mild cognitive impairment had Braak stage III or IV disease, whilst 22% of people with frank dementia were in Braak stage I or II. In addition, there was a strong association of atherosclerosis to mild cognitive impairment. In the absence of macro-pathological stroke disease, there was an odds ratio of 4.29 (95% CI 1.39-13.21) of having mild cognitive impairment in those with severe atherosclerosis in the Circle of Willis.

The Nun Study results taken along with the findings of the CERAD collaborators and MRC CFAS suggest several things. Firstly, in people with abundant neurofibrillary tangles and amyloid plaques, the additional burden of vascular lesions leads to poorer cognitive performance and an increased likelihood of dementia. Secondly, the presence of either Alzheimer's or vascular lesions as a single pathology seems to have weaker relation to cognitive performance. Thirdly, mixed pathologies in people with dementia are extremely common. Lastly, in the Nun Study at least, the vascular link did not seem to be mediated via *APOE* ε4 and is not necessarily related to visible stroke disease. These findings imply that the two pathologies at the very least have an important interaction, if not a causative link. Skoog (1998) suggests that

those who develop dementia after stroke have similar risk factors for AD (i.e. increasing age, less formal education, family history of dementia and cortical atrophy). Thus, stroke disease certainly modifies the clinical expression of AD. It may be that vascular lesions 'unmask' incipient dementia, which would be in keeping with the cognitive reserve theory (Satz, 1993; Stern, 2002).

Another argument for an important vascular link with AD would be in the demonstration of a scarcity of 'pure' VaD. Nolan et al. (1998) looked at 87 subjects recruited from a specialty dementia clinic. Diagnosis of dementia subtype was based on NINDS-ADRA criteria, taking into account the modified Hachinski Ischemia Scale. Importantly, the neuropathological diagnosis of VaD could not be made in a single case. Where there was a clinical diagnosis of AD, there was actually mixed dementia in 14/42 (33%) of cases. There was mixed disease in 100% of those who had a presumptive diagnosis of VaD and where the ante-mortem diagnosis was mixed dementia, in fact the diagnosis was pure AD in 4/13 (31%). These results could be because of selection bias. The authors take care to point out that stroke alone may still lead to dementia. However, even if this group were highly selected, this makes the prevalence of mixed disease all the more remarkable. Lim et al. (1999) published results from an autopsy series tending to suggest similar results, that vascular lesions as a single cause for dementia are extremely rare.

Autopsy studies have therefore demonstrated a strong and ubiquitous relation between vascular and Alzheimer's pathology.

Possible mechanisms linking vascular factors to AD and cognitive impairment

As already discussed, the link between vascular factors and cognitive impairment is not necessarily causal. A plausible biological mechanism, which could be tested

scientifically, would strengthen this argument. Diabetes, ischaemic heart disease, stroke and hypertension are among the vascular risk factors associated with cognitive decline (table 1.2). These may affect the brain in differing ways. Thus the absence of a common pathway of ischaemia to cognitive decline does not prove that there is no link.

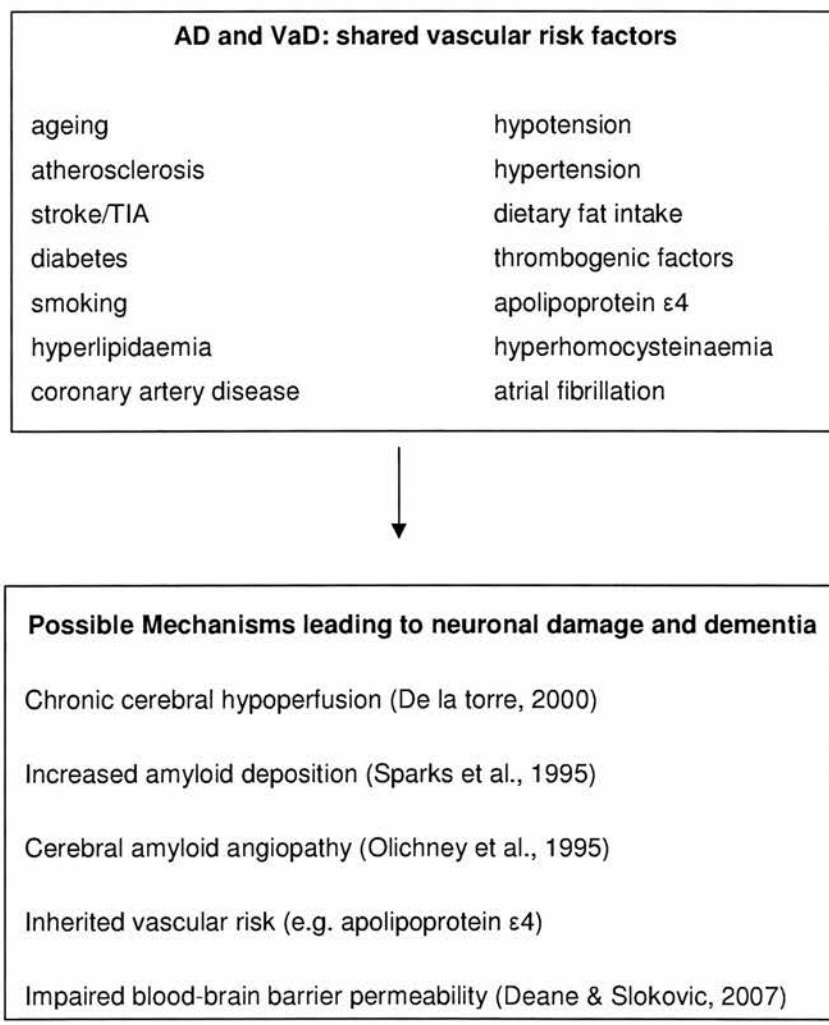
Different groups have looked at possible biological mechanisms. Coronary artery disease may be associated with increased numbers of neuritic plaques (Sparks et al., 1995). The same authors showed that there were increased numbers of neurofibrillary tangles in people with hypertension, even in the absence of dementia. Animal studies have shown an increased β–amyloid production in rodent hippocampi following transient ischaemia (Hall et al., 1995). Thus there would appear to be a possible mechanism of developing Alzheimer pathology in response to vascular insult. There are a variety of possibilities as to precise causes. Amyloid deposition, which presumably originates from vascular rather than neuronal tissue (Iwamoto et al., 1997), has been associated with hypertension and ischaemic stroke (Olichney et al., 1995). It has been suggested that this is caused by a direct toxic effect of β-amyloid on vascular endothelium (Sutton et al., 1997). Suggested mediators of this toxic damage are oxidative stress (Mattson et al., 1995) and free radical damage (Li & Forstermann, 2000).

The ε4 allele of the *APOE* gene is associated with both AD and VaD, as well as a variety of other vascular conditions (Davignon et al., 1988; Hofman et al., 1997; Slooter et al., 1997). It would seem perfectly logical to assume that this is the link between vascular disease and AD. This may be the case, but the Nun Study found no link – there was no association of lacunar or cortical infarcts to *APOE* status (Snowdon et al., 1997), though as already noted the results of the Nun Study may not be generalisable due to the select study population. It has also been noted that the relationship of apolipoprotein ε4 to AD is stronger than its association to VaD (Sulkava et al., 1996; Ross et al., 1999). Ross et al. (1999) argue that the high prevalence of dementia in people with vascular disease who are homozygotic for ε4

may in fact be due to the concomitant presence of AD and is not simply related to VaD.

Figure 1.1 shown below shows a sketch of the vascular risk factors shared between AD and VaD and the mechanisms linking these to AD. It is to be postulated that the mechanisms leading to 'dementia' in AD are also lined to 'dementia' in VaD

Figure 1.1: sketch of shared vascular risk factors and possible mechanisms



It must be stated that all of the above mechanisms at the moment are at the stage of being plausible theories. This then means that based on current evidence no definite conclusions can be drawn on the direction and causality of the links between vascular factors and AD. Clearly, more work is required to test specific hypotheses before a definite, strong and causal link is identified. It remains a possibility that vascular disease and AD are linked by chance, or by an independent factor. A separate theory, that vascular disease 'unmasks' AD allowing the clinical diagnosis of dementia, may also be true.

Conclusion: vascular factors in AD and dementia

It has been argued that what we now consider to be late-onset AD is in fact a multi-factorial disorder, with an important vascular component, and this is especially true in people of old age (Breteler, 2000b). Several strands of evidence point towards this being the case. Most importantly, there are good autopsy data showing that Alzheimer's disease and vascular disease are frequently found to co-exist in the brains of people with dementia. This must be coupled with a wealth of epidemiologic evidence linking 'vascular' risk factors to cognitive decline and AD. In addition there is a lack of good clinical features to readily distinguish AD and VaD. In the search for a cause of AD, separating dementia into VaD and AD may be unhelpful: "it is very likely that much of the reported data about vascular dementia is in fact about mixed disease, albeit not yet recognised as such" (Bowler & Hachinski, 2003b, p. 329).

All in all, there is strong support for the suggestion that AD may have a vascular cause. This has been highlighted in this section as it is of great interest in the mechanism of any link between childhood mental ability and risk of dementia. Whalley & Deary (2001) linked lower mental ability to excess mortality risk. In discussing possible mechanisms, they put forward several putative theories. To

summarise, IQ could be a marker of integrity of the organism or it could also reflect the fact that people of differing IQ may have differing health risk patterns, an element of which may be behavioural. In particular this includes health related behaviours such as smoking. These theories of mechanisms may provide insight into possible mechanisms linking lower mental ability and late-onset dementia. The latter theory outlined above is possibly the more appealing from a medical point of view; if there is a vascular link it promises more in terms of possible future intervention strategies.

Part 2. Methodology of the Scottish Mental Survey 1932

Studying mental ability prior to the onset of ageing-related decline is of vital importance in the study of individual differences in cognitive ageing. The Scottish Mental Survey 1932 (SMS1932) is of unique status in this field in that it permits the investigation of cognitive changes between childhood and old age. This chapter aims to outline the general methodology employed in the follow-up studies of the SMS1932, which are of central importance to this thesis and hence merit a detailed description here. In subsequent parts of this thesis, specific details on the methodology will be discussed where relevant. These more detailed aspects will benefit from the general description contained in this chapter.

Description of original Scottish Mental Survey 1932

The Scottish Council for Research in Education (SCRE) undertook the task of measuring mental ability in an entire birth year of Scottish children. The aim of the study was to describe the "distribution of intelligence throughout the community" (SCRE, 1933) in order to estimate future educational needs and thus plan educational service provision. For practical reasons "Scotland's Mental Survey Committee", found it so difficult to select a representative sample that they made plans to test the whole nation. On the 1st June 1932, virtually every child at school in Scotland who was born in the calendar year 1921 sat down to take this group-administered test. Some were tested a few days later. Standard instructions were given in every participating school. In total 87,498 children (44,210 boys and 43,288 girls) took the test, representing over 95% of the relevant population. The test used was a version of the Moray House Test No. 12 (MHT), which had been used previously as an 'eleven-plus' test for selection into secondary education. It consists of 71 items in categories including following directions, same-opposites, analogies, reasoning, arithmetical,

spatial, mixed sentences and proverbs. The maximum possible score is 76. To assess the criterion validity of the MHT, a random subset of the birth year (500 boys and 500 girls) were given the Stanford-Binet test, administered by individual testers. The correlation between the Stanford Binet test and MHT was 0.81 for boys and 0.78 for girls (SCRE, 1933), thus validating the MHT as a test of general mental ability.

The results of the SMS1932 were recorded in hand-written ledgers based on geographical area, and recorded the pupils' names, schools and MHT scores. These ledgers are stored at the Scottish Council for Research in Education. The data were transcribed onto a computerised database. This database was made available by SCRE to the research team involved in follow up studies of the SMS 1932.

Follow up studies of the SMS1932

The SMS1932 was initially planned as a piece of educational research, aimed at informing educational policy decisions. Over half a century later these data became useful in the study of cognitive ageing. Having data from age 11 coupled with follow-up of subjects now aged approximately 80 allowed the study of cognitive abilities across a gap representing almost the whole human lifespan (Deary et al., 2000). The second use of the data was to investigate the association between mental ability in childhood to health states in later life. This was done in two ways – by recruiting survivors of the SMS1932 and by utilising existing public health records such as data on hospital discharges held by the Information and Statistics Division of the NHS in Scotland.

This research program using data from the Mental Survey of 1932 was planned and executed in two areas of Scotland, in Aberdeen and in Edinburgh. Subjects were recruited in these areas to form so-called 'birth cohorts', the Aberdeen Birth Cohort 1921 (ABC1921) and the Lothian Birth Cohort 1921 (LBC 1921). Although similar

in philosophy and aims, they employed different methodologies and both are therefore described separately below, prior to summarising their results in a single section.

The Aberdeen Birth Cohort 1921 (ABC1921)

The research team began recruitment of local survivors of the SMS1932 in January 1998. Participants were identified using the Community Health Index (an NHS register of patients on General Practitioner's lists). After approval from the local ethics committee, 199 subjects were contacted, along with a further 35 people who volunteered after hearing about the study by 'word of mouth' or from media reports. Of these 234 potential subjects, 208 agreed to a full physical and mental health assessment. One hundred and one of the group agreed to re-sit the original MHT, and 73 of these did so as a group on June 1st 1998 (precisely 66 years following the original test) in a public hall specifically booked for this purpose. The remaining 28 re-took the MHT over the proceeding 5 months. The repeated MHT involved two very minor changes to test questions; one question replaced the archaic word "vitamine" with "vitamins", and a question referring to "pounds, shillings and pence" was changed to refer to "feet and inches". In addition to re-sitting the MHT, the participants undertook a cognitive battery including MMSE (Folstein, Folstein & McHugh, 1975), NART (Nelson, 1982), Raven's progressive matrices (Raven et al., 2001) and the Digit Symbol and Object Assembly tests from the Weschler Adult Intelligence Scale-Revised (WAIS-R; Weschler, 1981). These tests are described in table 1.3, below. Detailed socio-economic information such as Carstairs index (Carstairs & Morris, 1991) years of education and parental occupation was recorded using standard forms. Physical data were also recorded including demi-span, height and weight to name a few. Since 1998, the ABC1921 has been followed up in further waves, with medical assessment and psychometric testing.

The Lothian Birth Cohort 1921 (LBC1921)

The Edinburgh based research team expanded upon the ABC1921. The LBC 1921 recruited subjects between September 1999 and July 2001. They were found through the Community Health Index for Edinburgh and using advertisement in local and national press. A total of 550 healthy community dwelling individuals (234 men, 316 women) volunteered to take part in the study.

Each participant underwent physical and cognitive testing at the Wellcome Trust clinical research facility at the Western General Hospital in Edinburgh. Basic medical history, including self-reported disease history and medication history, was recorded. Trained nurses performed physical testing including blood pressure, basic lung function, height, weight, demi-span, visual acuity and 6 metre walk test. Blood was taken for biochemical, haematological and genetic assays. A 12 lead ECG was recorded at this visit. Trained researchers carried out cognitive testing at the same visit. Table 1.4 shows the tests used with a brief description of each test. A more complete description of some of the cognitive tests is found elsewhere in this thesis where relevant.

Table 1.4: A brief description of cognitive tests used in the LBC1921

Name of test	Brief description of test
Moray House Test (MHT)	As above.
MMSE	A tool designed to screen for possible dementia. Scored out of 30, a score of less than 24 is conventionally taken as indicative of cognitive impairment.
Raven's Progressive Matrices (RPM)	Measures non-verbal reasoning. Consist of 60 items (organised in 5 groups of 12) with test lasting 20 mins. Participants are shown an incomplete pattern and are asked to complete the pattern by picking the most appropriate response from a list.
Verbal Fluency	Said to be a test of executive functioning (Lezak, 1995). Participants are asked to name as many words as possible beginning with the letters C, F and L. Subjects have 1 minute for each letter.
Logical Memory	A test of verbal declarative memory. From the Weschler Memory Scale-Revised (Wechsler, 1987). Subjects are read aloud 2 short stories (story A and story B). Immediate (free recall) and delayed recall (after 30 minute interval) of the ideas contained in these stories are measured. The combined score of immediate and delayed recall for both stories gives a score for Total Logical Memory (score out of 100).
National Adult Reading Test (NART)	A pronunciation based assessment of prior or 'pre-morbid' cognitive ability. Participants are shown a list of 50 irregular English words and are asked to read them aloud. Failure to pronounce the word correctly results in an error. Traditionally scored as a number of errors, the LBC scored as the number of correct items as a pragmatic decision to ensure that all inter-correlations between cognitive tests scaled in the same direction. This test is used for premorbid IQ estimation.

Summary of important findings of Scottish 1921 birth cohorts

Numerous publications have arisen from follow up studies of the SMS 1932 (Whalley & Deary, 2001; Deary et al., 2001; Deary et al., 2002; Deary et al., 2003b). Notable examples include work that has demonstrated the association of cerebral white matter lesions to IQ in childhood and in later life (Deary et al., 2003a; Leaper et al., 2001) and the contribution birth weight makes to childhood IQ independent of social class (Shenkin et al., 2001). Possibly the most important papers from the 1921 birth cohorts are summarised below.

Stability of intelligence from age 11 to age 77

The Aberdeen Birth Cohort was used to report the longest follow up study of individual differences in psychometric intelligence at the time of being published (Deary et al., 2000). In the ABC1921, the mean score on the MHT in 1932 was 43.3 (SD = 11.9), whilst in 1998 the same subjects had a mean score 54.2 (11.8). ANOVA showed the effect of time on MHT scores to be significant ($F = 118.0$, $df = 1.99$, $p<0.001$) with people having a higher score at age 77. The raw Pearson's correlation between MHT in 1932 and MHT in 1998 was $r = 0.63$ (95% C.I. 0.50-0.74, $p<0.001$). This raw correlation was an underestimate due to attenuation of the variance in the re-tested sample compared to the SMS1932 population. The disattenuated correlation was $r = 0.73$. The correlation between MHT in 1932 and Raven's in 1998 was 0.48, which was not significantly different to the correlation between MHT in 1998 and Ravens, $r = 0.57$.

Of note here is that the LBC 1921 was able to replicate these results (Deary et al., 2004). They reported a raw correlation of $r = 0.66$ ($p < 0.001$) between MHT age 11 and MHT age approximately 80. The disattenuated correlation for the LBC1921 was identical to that of the ABC1921, $r = 0.73$.

These remarkable results – the disattenuated correlations indicate that about 50% of variance in test scores age 77 is explained by test scores at age 11 – were interpreted as demonstrating that, in the absence of significant physical and mental illness, psychometric intelligence shows high stability across virtually the entire human lifespan. Although the mechanisms underlying this stability (genetic +/- environmental) and by definition the reasons contributing to change over time cannot be assessed in this study, the results were important step in beginning to assess the sources of stability and change in cognition in older people. Additionally, if half the variance of intelligence is stable, then half the variance must represent change, allowing for investigation of the determinants of that change.

Relation of childhood ability to late life health status

Starr et al. (2000) explored the relationship between physical disease and cognitive function in old age. The disease status of the entire ABC 1921 sample (234 people) was ascertained from medical notes. Scores on MHT in 1932 were compared for specific disease categories e.g. hypertension, diabetes mellitus cerebrovascular disease. The only disease associated with a lower test score was dementia. The mean MHT score at age 11 for those with dementia was 32.8 (SD = 15.8) and the mean score for those without was 40.4 (SD = 13.0). However, both education ($F= 4.27$, $p = 0.002$) and occupation ($F = 4.27$, $p = 0.002$) were associated with MHT age 11. Once these socioeconomic variables were controlled for in an ANOVA model, there was no longer an association between diagnosis and MHT ($F = 0.06$, $p = 0.81$). This paper failed to demonstrate a link between any other diagnosis and childhood mental ability. There was a correlation between MHT score at age 11 and the Barthel Index (Mahoney & Barthel, 1965) $r = 0.24$, $p = 0.001$, even after using general linear modeling to control for MMSE (beta = 0.21, $p = 0.003$). The Barthel Index is a widely used 10-point scale that measures activities of daily living. It is considered to be the gold-standard generic disability measure (Hobart et al., 2001). This correlation between MHT and Barthel Index implies that childhood ability is linked to functional

independence in old age, corroborating the finding from the Nun Study (Snowdon et al., 1989) that sisters with degree level education were more likely to be living independently when compared to nuns with less education (OR=2.67, 95% CI 1.16-6.16).

Starr et al. (2000) concluded that "the diagnostic approach" (i.e. comparing childhood ability in people with specific disease acquired later) was not particularly useful in old age. There may be reasons why it did not detect differences. Firstly, a cohort effect could not be excluded. The ABC subjects were relatively healthy, meaning that numbers in each category were small (e.g. only 12 had cerebrovascular disease). This could reflect a degree of attrition (increased mortality in those with lower childhood ability). Similarly, by its very nature the study would tend to attract those with milder disease (e.g. those who had previously had a severe stroke would not be able to attend and undertake the rigorous cognitive and physical tests). Secondly, it may be that some people with disease were actually classed as healthy. For example, the Healthy Old People in Edinburgh (HOPE) study showed that some healthy subjects would actually have had hypertension if they had presented to medical services (Starr et al., 1996).

IQ age 11 and longevity

There are data establishing the influence of education and socio-economic status on morbidity and mortality. Social deprivation in childhood leads to increased rates of illnesses such as cardiovascular disease, respiratory disease stroke, lung cancer and stomach cancer (Davey Smith et al., 1998a; Joseph & Kramer, 1996). In addition to the Nun Study's finding of increased longevity in nuns educated to a higher level (Snowdon et al., 1989), Davey Smith et al. (1998b) demonstrated that the age at which people leave full-time education relates to cause specific and all cause mortality. The SMS1932 allowed for the first time an actual measure of childhood

ability to be assessed as a predictor of mortality (Whalley & Deary, 2001). There were 2792 children born in Aberdeen attending school, with 2230 (79.9%) being traced using public and health records as "alive" (n = 1101), "dead" (n = 1084), "untraced" (n = 562) or "moved away" (n = 45) on 1st January 1997. The MHT score was converted to an IQ type score (mean = 100, SD = 15) controlled for age in days. People who had died had a lower IQ age 11. This result was also demonstrated when men and women were analysed separately. Cox's proportional hazards regression showed that childhood IQ was significantly associated with survival (change in survival expectancy 0.9847 per unit change in IQ, $p < 0.001$). Thus, for example, if a 2SD difference in IQ was compared (i.e. 85 vs. 115) then the mean chance of survival in the lower group compared to the higher group is 63% (95% CI 56-71%). Whalley and Deary then used a measure of overcrowding for school areas (defined at the Scottish Census of 1931) as a marker of deprivation. Partial correlation controlling for overcrowding did not change the association between childhood IQ and survival.

This paper concluded that the mechanisms underlying this association were unknown, but put forward several putative theories. The effect could be seen as IQ representing a record of bodily insults (or conversely a marker of integrity of the organism). It could also reflect the fact that people of differing IQ may well adopt differing health behaviours. An additional theory was postulated that childhood IQ could predict entry into safer employment environments. This paper's final conclusion was that childhood mental ability should be taken into account by future studies investigating inequalities in health and mortality.

Genetic influence on cognitive change over the life-span

The *APOE* gene is a risk factor for AD and heritable influences on cognition may be greater in old age (Plomin et al, 1997; Farrer et al., 1997; Breitner et al., 1999). Two papers looked at the contribution of this gene to individual differences in 'normal'

cognitive ageing from age 11 to age 80. The analyses performed first were on the ABC1921 (Deary et al., 2003). One hundred and seventy three participants in the ABC gave a DNA sample which was genotyped for *APOE* status (ε2, ε3 or ε4). To summarise the results, although allele frequencies were similar to larger, more representative samples, no main effect of gene status on cognition at age 11 (measured by MHT) or at age 77 (measured by Raven's Progressive Matrices) was found. However, the authors concluded that the sample was underpowered to detect very small differences.

The LBC1921 was able to essentially perform the same study as the ABC1921, this time with larger numbers and the participants were 3 years older when they underwent cognitive testing in old age (Deary et al., 2002). All people with a pre-existing diagnosis of dementia or who had an MMSE of < 24 were excluded. They were able to determine the *APOE* genotype for 466 subjects who had an IQ score at age 11 and again at age 80. The mean score at age 11 was 99.4 (SD = 15.2) in those who were ε4 +ve, and 100.8 (SD = 14.4) in those who were ε4 –ve. There was no significant difference between these scores. The IQ at age 80 was 97.0 (SD = 15.7) for those who were ε4 +ve, and was 101.1 (SD = 14.2) for those who were ε4 –ve. At age 80, there was a significant difference between the two groups ($t = 2.64$, $p = 0.009$). Cardiovascular disease history was not associated with cognitive change and medication type or number did not differ in those with and without the ε4 allele. Again, the ε4 frequencies were similar to other samples. Although the effect of *APOE* ε4 on IQ change across the lifespan is small, the results are of major importance because "Identifying a factor that influences non-pathological, lifetime cognitive change has large public health implications because, in the absence of a sharp risk threshold, most adverse events – and most of the personal and economic burdens that these bring – occur to old people who are within the 'normal' part of the distribution" (Deary et al., 2002, p. 932).

I have concentrated here on the *APOE* gene as this has had much research interest in recent years. However, in this rapidly advancing field, the follow-up of the SMS

1932 has yielded many results of interest in the field of the genetics of cognitive ageing (Visscher et al., 2003; Deary et al 2005a; Deary et al., 2005b; Harris et al., 2005; Kachiwala et al., 2005; Thomson et al., 2005; Deary et al., 2006; Harris et al., 2006). It is beyond the scope of this thesis to go into detail of these specific genetic issues.

Part 3. Childhood mental ability and dementia

It is likely that factors that influence mental ability in later life are also present in childhood. There are a number of reasons to suspect that early life factors may have an important impact on later susceptibility to dementia. It has been recognised that there is a link between educational level and risk of dementia (Evans et al., 1993; Stern et al., 1994; Plassman et al., 1995; Mortel et al., 1995; Schmand et al., 1997; Zhang et al., 1990; Fratiglioni et al., 1991; D'Arcy, 1994; Mortimer & Graves, 1993). Socio-economic status may also be associated with differing trajectories of cognitive ageing and risk of dementia (Evans et al., 1997; Karp et al., 2004; Wilson et al., 2005), possibly with a complicated relationship between socio-economic status and educational status.

This part of the thesis first describes the literature on childhood mental ability and its association with risk of dementia. I then discuss the role educational level has in the risk of dementia. This introductory chapter finishes by describing possible mechanisms of how childhood mental ability and/or educational level might be linked to dementia.

Childhood mental ability and risk of late life dementia: follow up of the SMS1932

Important data looking at the risk of dementia in people of differing mental abilities have come from a follow up study of the SMS1932. The investigators from the ABC tested if there was a link between childhood mental ability and dementia by undertaking a case-control study.

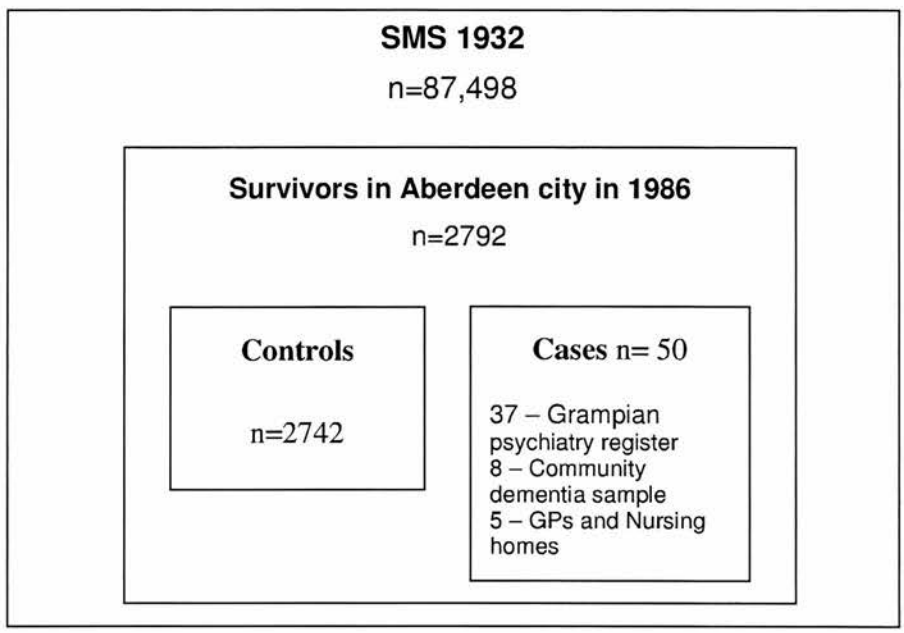
Whalley et al. (2000) identified cases with late-onset dementia from three areas. Firstly, the Grampian Psychiatric Case Register was examined; this had been

established in 1963 as a record of all inpatient and outpatient contacts with psychiatry services. This identified 75 possible cases. Subjects were excluded (n=38) if the onset of disease was before age 65 or if the dementia was thought to be caused by disease other than AD or VaD, leaving 37 definite cases. Secondly, the ABC organised a community dementia sample. In 1998, 519 community dwelling residents of Aberdeen who had taken the SMS1932 were traced. After establishing no contra-indications to contacting these people, 291 (56%) were randomly contacted, with 262 (90% of those contacted) consenting to take part in a survey of physical and mental health. As part of this survey, subjects had demographic data collected, had some medical information collected including risk factors for vascular disease, underwent a physical examination and had an MMSE recorded. Where the MMSE was suggestive of dementia (here defined as a score below 24) a more detailed systematic clinical review was undertaken. This led to 8 people being diagnosed with dementia using ICD-10 criteria. Lastly, an additional 5 cases who met ICD criteria for a diagnosis of dementia but who were unknown to medical services were identified from local GP's and nursing home managers. In total, 50 definite cases with late-onset AD were identified.

The cases were compared to a community control group. This was made up of all the people in Aberdeen city born in 1921 who had taken part in the SMS1932. Public health records were used to trace children who had an MHT score available on the SMS1932 database, and it was ascertained whether these individuals were alive or dead using the register of births, deaths and marriages. The researchers therefore compared MHT scores in those cases and controls who were alive and living in Grampian at various time points between 1986 (when cases and controls would be 65 years old) and the end of the study in 1997.

This complicated methodology is summarised as a diagram below (figure 1.2).

Fig 1.2: Summary of cases and controls used in case-control study of childhood mental ability and dementia in the ABC1921 (Whalley et al., 2000)



At age 11, those children who later developed dementia had a lower MHT score than the population controls. The mean MHT for cases (n=50) was 32.1 (95% CI 27.6-36.6) and for the population controls (n=2742) MHT = 36.2 (95% CI 35.7-36.7), $p<0.03$.

Interestingly, this study identified an important finding unrelated to the initial hypothesis. There were important significant differences between MHT scores in those who had migrated out of Aberdeen City compared to those who had stayed. The mean MHT score for those who stayed in Grampian (n = 1082) was 34.2 (95% CI 33.3 – 35.0) compared to those who had migrated out of Aberdeen n=833) who had a mean MHT of 37.2 (95% CI 36.3 – 38.1; $p<0.001$).

The finding of lower mental ability in cases might have been affected by two main biases. The control group of 2742 children born in Aberdeen contained people who would not survive into the risk period for developing late-onset AD and thus be

biased by a survival effect (i.e. the association between mental ability and longevity). The control group additionally contained many people who had moved out of Grampian region. Hence there may have also by an effect of migration, with the control group having a higher mean MHT because it contained people who later moved out of Grampian region. This was the rationale behind comparing MHT scores in cases and controls who were alive and living in Grampian at different time points between 1986 and 1997. The mean MHT scores in these groups are presented in table 1.5, adapted from Whalley et al. (2000).

Table 1.5: Mean MHT scores in survivors of SMS1932 compared in people with and without dementia

	Cases (dementia)		Controls (no dementia)		
	n	Mean MHT (95% CI)	n	Mean MHT (95% CI)	Sig
Alive in 1932	50	32.1 (27.6-36.6)	2742	36.2 (35.7-36.7)	p<0.03
Alive in 1986	50	32.1 (27.6-36.6)	772	35.3 (34.3-36.2)	p=NS
Alive in 1992	48	32.0 (27.3-36.7)	661	35.7 (34.7-36.8)	p=NS
Alive in 1993	45	31.0 (26.1-36.0)	639	35.8 (34.7-36.8)	p<0.03
Alive in 1995	41	31.2 (26.0-36.3)	586	36.1 (35.1-37.2)	p<0.03
Alive in 1997	34	29.6 (24.4-34.8)	552	36.2 (35.1-37.3)	p<0.01

These results show that there is indeed a lower score observed in the mean MHT of people with AD when compared to those without, confirming the association between lower mental ability in early life and late-onset dementia (Snowdon et al., 1996; Evans et al., 1993; Stern et al., 1994; Plassman et al., 1995; Mortel et al., 1995; Schmand et al., 1997). The authors interpreted these data as "support for a link

between age-related brain changes and late-onset dementia in which the link is modified by childhood mental ability" (Whalley et al., 2000, p. 1458).

A problem with accepting these results is that there is no ready explanation as to why the difference in MHT between the groups evident at age 11 disappears when the two groups are compared at age 65 only to re-appear when the groups are age 72. The association at age 11 could be due to bias caused by survival and migration as discussed above. An important possibility to consider for the lack of association when the groups are aged between 65 and 72 is overmatching. There is clearly a very complex relationship between the many factors that influence mental ability (e.g. age, socio-economic status, nutritional status and presence of diseases). It may be that the cases and control groups are so well matched on the precise factors that influence the individual differences in mental ability that we are unable to find a difference in this ability when it is measured. Why then should the difference in MHT 'reappear' when both cases and controls are older? As has already been discussed, it has been hypothesised that genetic influences on cognitive ability are more important in older subjects (Plomin et al, 1997). Thus, when the subjects were older, there were sufficient differences in the factors contributing to mental ability between the two groups to allow a difference in this mental ability to be measured.

This follow-up study of the SMS1932 is of tremendous value in evaluating a link between lower childhood mental ability and late-life risk of dementia. Central to this value is the use of the MHT, a true, valid measure actual prior mental ability. Before this study, there had been no valid measures of actual prior mental ability measured in childhood that were available for virtually an entire birth year. People had studied other markers such as number of years of education and socio-economic status and their relationship to cognition in later life. The results of some of these publications are discussed below after first discussing another important research programme, the Nun Study.

Early life mental ability and risk of late life dementia: the Nun Study

The Nun Study is a well conducted longitudinal study of ageing and Alzheimer's disease. It is called the Nun Study as the study population were recruited from nuns belonging to a religious order, the School Sisters of the Notre Dame, who were born in the USA before 1917. Of a possible eligible population of 1027 nuns, 678 (66%) volunteered to take part. The participants agreed to take part in annual assessment including a cognitive battery of seven neuropsychological tests (including memory, concentration, language, visuo-spatial ability, orientation to time and place), physical examination and certain blood tests.

This study is especially notable in that all of the participants agreed to donate their brain for post-mortem examination as part of a clinico-pathological study of the ageing brain. The study collaborators had access to convent archives, which contained a host of important information relating to possible risk factors for cognitive decline in later life. Examples of such data were socio-economic information for the subjects and their families, educational achievements attained and demographic data. These data were available for the entire time period from the sisters' entry into the order until their death.

The Nun Study is a truly remarkable study and has published very widely in the field of cognitive ageing. This diversity in research questions has included brain imaging (Mortimer et al., 2004; Gosche K et al., 2002; Smith et al., 2000), pathological findings in dementia (Riley et al., 2002), links between brain infarction and AD (Snowdon et al., 1997) and the relationship of early life mental ability to independent functioning (Greiner et al., 1996) and longevity (Snowdon et al., 1999).

Snowdon et al. (1996) investigated early life mental ability and later risk of dementia in a subset of participants of the Nun Study. The measure of early life mental ability used in this study was a composite score based on linguistic ability. Prior to taking

their religious vows, nuns were asked to complete a short essay to "include the place of birth, parentage, interesting and edifying events of one's childhood, schools attended, influences that led to the convent, religious life, and its outstanding events" (Snowdon et al., 1996, p. 529). The mean age at writing of the autobiography was 22. These autobiographies were stored in the convent archive and were made available to the Nun Study collaborators. Only handwritten essays were used to exclude typewritten essays having been written by someone else. Between 1931 and 1939, 103 nuns from Milwaukee province wrote an autobiography. Of these, hand-written autobiographies were located for 93 (90%) of the nuns.

Linguistic ability was calculated from 2 aspects of the autobiography: idea density (Kintsch & Keenan, 1973; Turner & Greene, 1977) and grammatical complexity (Cheung & Kemper, 1992). The basis for using these two constructs as a marker of mental ability was that "Prior studies suggest that idea density is associated with educational level, vocabulary, and general knowledge, whereas grammatical complexity is associated with working memory, performance on speeded tasks, and writing skill" (Snowdon et al., 1996, p. 529). The mean idea density (ID) and grammatical complexity (GC) scores were computed for the last 10 sentences of each autobiography. Autobiographies were scored for ID and GC by a single examiner who was blind to the late life cognitive status of the subject. The reliability of scoring was checked by 10 autobiographies being scored by an independent investigator. Although the intercoder correlation is quoted as 0.88 for idea density and 0.93 for grammatical complexity, no statistical significance is reported.

Examples of sentences taken directly from two nuns' autobiographies are shown in figure 1.3, adapted from Snowdon et al. (1996). This figure gives an illustration as to how ID and GC are calculated. In these examples Sister A scored lowest on both ID and GC whilst Sister B scored highest.

Figure 1.3: Two examples of autobiographies used to calculate idea density and grammatical complexity, adapted from Snowdon et al. (1996)

Sister A	Sister B
I was born in Eau Claire, Wis, on May 24, 1913, and was baptized in St. James Church. (ID=3.9; GC=0)	The happiest day of my life so far was my First Communion Day which was in June nineteen hundred and twenty when I was but eight years of age, and four years later I was confirmed by Bishop D.D. McGavick. (ID=8.6; GC=7)
Two of the boys are dead. (ID=3.3; GC=0)	I visited the capitol in Madison and also the Motherhouse of the Franciscan Sisters of Perpetual Adoration at Duluth which visit increased my love for Notre Dame, because it was and is Notre Dame. (ID=9.1; GC=7)
I prefer teaching music to any other profession. (ID=5.0; GC=5)	Now I am wandering about in Dove's Lane waiting, yet only three more weeks, to follow in the footprints of my Spouse, bound to Him by the Holy Vows of Poverty, Chastity and Obedience. (ID= 9.1; GC=7)

There was a significant correlation between ID and GC ($r=0.45$, $p<0.001$) and a significant correlation between ID and years of education ($r=0.27$, $p<0.01$). No correlations were presented for GC and years of education.

Regression analyses were performed relating early life mental ability in early life, age and years of education to the MMSE (used here as a marker of 'global cognitive functioning'). Higher scores on idea density and grammatical complexity were associated with higher MMSE scores, with idea density having the strongest association as measured by percentage of variance (r^2). Similar results were found in a sub-group of this sample who were all teachers with a bachelor's degree ($n = 85$).

Linguistic ability was also associated with poor performance on neuropsychological testing. The nuns' performance on linguistic ability was categorised as low if they fell into the bottom tertile of results and high if they fell into the highest two tertiles. After adjusting for age at cognitive testing and years of education there remained a strong relationship between most of the cognitive tests and linguistic ability. Adapted from Snowdon et al. (1996), table 1.6 shows the adjusted odds ratios for prediction of

poor performance on cognitive tests in low versus high performance in linguistic ability.

Table 1.6: Odds ratio for prediction of poor performance on test of cognitive function in low versus high linguistic ability groups in subjects in the Nun Study

Linguistic ability	Cognitive test	Adjusted OR (95% CI)	Sig
ID	MMSE	30.8 (2.6-362.7)	p<0.01
	Delayed word recall	15.3 (3.0-78.3)	p<0.001
	Word recognition	15.8 (1.8-138.3)	p<0.01
	Word list memory	8.9 (1.7-47.2)	p<0.01
	Verbal fluency	7.3 (1.2-42.8)	p<0.05
	Constructional praxis	5.4 (1.0-30.7)	p=NS
	Boston naming	3.2 (0.7-15.4)	p=NS
GC	MMSE	16.3 (2.0-130.9)	p<0.01
	Delayed word recall	4.1 (1.0-16.5)	p<0.05
	Word recognition	3.8 (0.8-19.1)	p=NS
	Word list memory	3.5 (0.8-16.0)	p=NS
	Verbal fluency	2.7 (0.5-13.3)	p=NS
	Constructional praxis	2.7 (0.5-13.4)	p=NS
	Boston naming	8.1 (1.5-45.2)	p<0.05

In this paper, the authors also analysed the linguistic ability in the nuns who had died. Of the 14 people who had died, five had pathologically confirmed AD based on Braak staging (Braak & Braak, 1991). Low idea density was present in 100% of those with AD, whilst none of the nuns who had normal brains at post-mortem had low idea density ($p<0.001$). Neuropathological examination showed a higher number of neurofibrillary tangles in the hippocampus and neocortex of those with low idea density compared to those with higher idea density.

The authors interpret their data to "support a strong relationship between cognitive ability in early life, as indicated by linguistic ability, and cognitive function and Alzheimer's disease in late life" (Snowdon et al., 1996, p. 531). They also reason that the result is directly related to linguistic ability in early life rather than lifestyle and

environmental factors encountered in mid- and late-life. This is because the same associations were also present in a subset of nuns who were college educated and who shared the same occupation. This could imply that education or occupation did not confound the results. Additionally, the sisters shared very similar lifestyles: the subjects in this study shared reproductive and marital histories, similar social activities, similar alcohol and tobacco use, similar occupation and income and hence socio-economic status, similar housing, food preparation and consumption and similar access to health facilities.

There are several flaws with this particular paper. Firstly, it is very likely that the cognitive processes underlying 'linguistic ability' are measured by the cognitive tests used in the Nun Study battery; there is a positive correlation on many diverse tests of cognition (Spearman, 1904). Poor performance on these tests of cognition does not automatically mean cognitive decline and therefore it cannot be concluded that the association between poor linguistic ability and poor cognitive performance implies a higher risk of dementia. Correlation between the autobiographies and later cognitive test scores might just be due to the continuity of trait intelligence. Secondly, possibly the largest flaw in this paper is that there are no data presented on health status of the elderly nuns – in particular vascular risk factors and the presence of stroke disease. Such factors have a major impact on acquired cognitive decline and may well be associated with mental ability in early life. Lastly, the numbers of nuns who had died at the time of publication of this paper was very small and so the neuropathological data must be interpreted with this in mind.

Further findings from the Nun Study looking at early life linguistic ability, late life cognitive function and neuropathology were recently published (Riley et al., 2005). The study participants in this analysis were nuns from Milwaukee and Baltimore who had handwritten autobiographies available (n=180). As described above, they underwent annual cognitive assessment. The mean age at first testing was 80 (range 75-91) and the mean age at last testing was 86 (range 76-95). Subjects were split by the presence or absence of memory impairment as measured by performance on the

delayed word recall test. Within these two groups, subjects were further categorised as having mild cognitive impairment (impairment in one specific cognitive area), global cognitive impairment (impaired MMSE and/or activities of daily living) and dementia (impaired memory, impaired cognition in another domain, impaired daily functioning and evidence of decline over at least 6 months). By the time of publication of this paper, 90 of the nuns had died and had post-mortem brain examination.

Prevalence of low idea density was greater in people with memory impairment when compared to those with an intact memory. This prevalence increased with severity of cognitive impairment in both groups with intact and impaired memory. This was the case at both the first and last cognitive assessments in the study. The odds ratios for presence of low idea density are shown in table 1.7, adapted from Riley et al. (2005).

Table 1.7: Unadjusted odds ratios for prevalence of low idea density in autobiographies from the nun study (adapted from Riley et al. (2005)

	OR for low idea density (95% CI)	
Cognition	First exam	last exam
Memory intact		
Intact	1.0	1.0
Mild impairment	1.3 (0.5-3.3)	2.7 (0.8-8.8)
Global impairment	5.0 (0.6-39.4)	5.1 (1.1-23.9)*
Memory impaired		
Mild impaired	5.3 (2.0-13.9)***	7.4 (2.1-26.4)**
Global impairment	25.0 (2.7-235.4)**	9.0 (1.9-42.2)**
Dementia	45.0 (9.1-222.4)***	14.7 (5.0-43.5)***

*p<0.05; **p<0.01; ***p<0.001

There was no change in results after controlling for age and education. As can be seen from table 1.7 the differences in prevalence of low idea density only reached

statistical significant difference in the group who were memory impaired, and in the group with intact memory but globally impaired cognition but only at the final testing and not the first testing.

The neuropathological data presented in this paper were also interesting. People with low idea density had lower brain weights. The mean weight for those with low idea density (n=39) was 1060g (SD=1014-1105) and for those with high idea density (n=51) was 1158g (SD=1118-1198), $p<0.01$. Logistic regression revealed that low idea density was more likely to be found in those with a brain weight of less than 1000g (OR = 12.2, 95%CI 2.6-58.5) and in those who met the pathological criteria for AD (OR = 3.7, 95%CI 1.4-10.3). There was a greater severity of AD pathology in those with lower idea density. However, this was only for neurofibrillary tangles in the neocortex and hippocampus: there was no difference in plaque pathology between those with high versus low idea density. The authors also looked at whether brain infarcts were associated with idea density; they found that large infarcts, lacunar infarcts and circle of Willis atherosclerosis were all more frequent in people with low idea density, but these differences were not statistically significant.

This paper presents compelling evidence that there is an association between low idea density and higher risk of dementia – there was an odds ratio of 45.0 (95%CI 9.1-222.4) of finding low idea density in those with clinically diagnosed dementia when compared to those with intact memory. The finding is consistent at repeated intra-individual assessment, being present at both the first and last cognitive assessments.

There also seems to be a 'dose-response'; the likelihood of low idea density increases with severity of cognitive impairment. This finding in particular requires closer scrutiny. If low idea density is a risk factor for AD and mild cognitive impairment represents early AD, then it should follow that low ID is found in similar frequencies in both AD and mild cognitive impairment. This does not seem to be the case: there was a lack of association between low ID and mild cognitive impairment in those

who had an intact memory (Table 1.7). These results can be interpreted in two ways. Firstly, it may mean that the low idea density found in those with dementia relates to the inter-correlation of neuropsychological tests rather than acting as a true risk factor. Secondly, it could cast doubt on the construct of mild cognitive impairment as an early form of AD.

Education, late-life cognition and risk of dementia

In their review of predictors of cognitive change in old age, Anstey & Christensen (2000) state "Education has proven to be the most important non-biological correlate of cognitive performance in many studies." (Anstey & Christensen, 2000, p. 163). There are a multitude of cross-sectional and case-control studies showing an association between fewer years of education and higher prevalence of dementia (Callahan et al., 1996; The Canadian Study of Health and Aging, 1994; Glatt et al., 1996; Ott et al., 1995). Even though they come from culturally disparate places such as Finland (Sulkava et al., 1985), Israel (Korczyn et al., 1991), China (Zhang et al., 1990), Italy (Rocca et al., 1990), France (Dartigues et al., 1991) and Sweden (Fratiglioni et al., 1991), studies show similar results. For example, The Canadian study of health and Aging (1994) found an odds-ratio of 4.00 (95% CI, 2.49-6.43) in those with less than 6 years of education when compared to those with greater than 10. There are, however, studies that do not find any association between education and dementia prevalence (Beard et al., 1992; Chandra et al., 1987; Shalat et al., 1987; Bonaiuto et al., 1995).

Gilleard (1997) sought to review the epidemiological studies relating education and dementia. Thirty-two papers were identified, from Canada, France, Italy, China, Holland, the USA, the UK and Sweden. Specific problems with many of the papers were highlighted that questioned the veracity of accepting the fact that fewer years of education is a risk factor for AD. For example, in the example cited above from the Canadian Study of Health and Ageing, there was deliberate oversampling of

institutionalised individuals, who were more likely to have dementia, but who also had significantly less education, raising the possibility of important bias.

Gilleard (1997) also highlighted a problem with accepting results the cross-sectional studies. The PAQUID study conducted in France initially showed a higher prevalence of dementia in those with less education (Dartigues et al., 1991). An incidence study (of all incident cases in the proceeding year) failed to show a difference in frequency of diagnosed dementia in those with less than 6 years education compared to those with more (Barberger-Gateau et al., 1993). Gilleard concluded from this that there was no definite evidence of a causal association between education and AD. However, one year is a very short period when studying incident dementia.

The PAQUID investigators have subsequently published data from a longer follow-up period (Letteneur et al., 1999). The initial PAQUID sample was randomly selected from electoral rolls. Of 5554 people contacted, a total of 3777 (68.0%) individuals who were 65 or older and living at home gave their consent to take part. A trained psychologist undertook a base-line interview. Data on years of education were recorded and categorised into 4 groups: no schooling, primary schooling (1-5 years), secondary schooling (6-12 years) and university education (> 12 years). A cognitive battery was performed. Dementia was diagnosed according to DSM-III criteria based on a questionnaire. Diagnosis was confirmed by clinical evaluation. The subjects were re-evaluated at years 1, 3 and 5. Cox's regression models were used to calculate hazard ratios. The referent group were taken as the group with high-school or higher education. The authors report a higher risk of AD in people with no education (HR=1.93, p=0.04) and primary school education (HR=1.49, p=0.02). The conclusion drawn from this is that the mental ability to pass a diploma (in this case a primary school diploma) provides a lower risk of the future diagnosis of dementia.

Cobb et al. (1995) presented data from the Framingham study which did not demonstrate an increase in incident dementia in those with less education. The

Framingham cohort were biennially examined, and from 1976 this included neuropsychological testing. Cases in the cohort were identified by clinical evaluation of a neurologist and neuropsychologist, based on an MMSE score of less than 24 or which had fallen by at least 3 points. DSM-III criteria defined the presence of dementia. Educational status had been recorded at the first visit 9in 1948-1950). It was recorded as 9 ordinal variables: no formal education, 4th grade or less, 5th-7th grades, grade school graduate, some high school, high school graduate, some college, college graduate and post-college education. These variables were further categorised as less than grade school, less than high school and high school graduate and beyond. In the Framingham cohort 60% of men and women had a high school diploma, which the authors thought was un-representatively high. Age was significantly associated with years of education: those with less education were older. The incidence of dementia in those with least education was double that of the most educated group. However, after controlling for age there was no longer an association between education and dementia. Comparing highest and lowest educational groups, the relative risk of AD was 1.04 (95% CI 0.62-1.74) and of "dementia" was 1.31 (95% CI 0.90-1.91). The only positive finding presented in this paper was a higher relative risk of non- Alzheimer's dementia (RR = 1.75, 95% CI 1.03-2.98) in those with least education compared to those with most.

The main conclusion drawn from the Framingham data was that low educational levels did not act as a risk factor for dementia or AD, but may be associated with 'non-Alzheimer's' dementia. Cobb et al. (1995) tried to explain the different results this study had achieved when compared to other longitudinal papers (in particular Stern et al., 1994). They re-analysed their data with age treated as a dichotomised variable (age groups 55-70 and 71-88). This changed the results: the relative risk of dementia in the lowest educated group was now 1.52 (95% CI 1.06-2.16). The authors claim that by not treating age as a continuous variable, important information gets contracted and that these results "underscore the importance of adequately adjusting for age." (Cobb et al., 1995, p. 1710).

Other longitudinal studies have shown an increased risk of dementia in those with less education. Ott et al. (1999) presented follow-up data from the Rotterdam study. They followed up 6827 people who had demographic data including educational level for an average of 2.1 years. Baseline neuropsychological testing was repeated. Diagnosis of dementia was confirmed at clinical and neuropsychological evaluation, or if the subjects had been admitted to hospital with a diagnosis of dementia. The authors grouped the educational levels into three groups high (at least 11 years of education), medium (7-10 years) and low (less than 7 years of education. Incident dementia was diagnosed in 137 individuals (71% AD, 13% VaD). There was an increased risk of dementia in women with lowest education (RR=2.1, 95% CI 1.1-3.9) and an increased risk of AD in this group (RR=2.0, 95% CI 1.0-3.9). There was no significant change in men. The authors could not explain this sex difference, although thought it unlikely to be due to the fact that there were more women than men in the study and that women in this population were less well educated. They could not exclude a cohort effect where in this group at least, years of education "represents a different quality for men than for women" (Ott et al., 1995, p. 665) and for women may be more reflective of socio-economic status.

The Kungsholmen project is a longitudinal study of ageing and dementia carried out in Sweden. Follow-up data from this have been reported looking at the effect of education on risk of dementia (Qiu et al., 2001). The initial study population were 2368 individuals older than 75 resident in the Kungsholmen district of Sweden. The base-line survey was in 1987-1989 and 1810 (76.4%) agreed to take part. Base-line data collected included demographic information (in particular years of education), testing on global cognitive function and medical history. Dementia was diagnosed on clinical grounds using DSM-III criteria. At base-line, 1296 individuals were dementia free and this group were used for incidence analyses. Of this group 313 died prior to follow-up, leaving a final 983 people who underwent comprehensive medical evaluation and were re-interviewed between 1991 and 1993. Cox regression was used to calculate relative risks of dementia and AD.

The educational level in this study was split into 3 groups: university level (≥ 11 years), high-school (8-10 years) and elementary (< 8years). There was a greater risk of AD in the group with least education (RR=2.7, 95% CI 1.4-5.0) and there was a greater risk of all types of dementia (RR=2.1, 95% CI 1.3-3.5). The increased relative risk of AD and dementia persisted after controlling for age, sex, MMSE and socio-economic status.

Cobb et al. (1995) used the Framingham data to test the hypothesis that fewer years of education was associated with a younger age at onset of dementia. This would imply a causative link, with less education causing a larger disease burden leading to an earlier age at onset. There were no differences in age at onset between the three educational groups.

Anstey & Christensen (2000) reviewed 14 longitudinal studies of cognitive change with 'normal' ageing that reported data examining the relation between years of education and cognitive decline over time. The authors found it difficult to draw formal conclusions. The reasons they cited for this mainly surrounded the various study designs employed. For example, years of follow-up ranged from 1 to 28, and the sample sizes ranged from 132 to 14,883. Cognitive outcome measures were also very varied including memory, fluid and crystallised intelligence measures, mental status and composite measures. Broadly the results fell into four groups: the rate of cognitive decline is less in more educated (Albert et al., 1995; Shichita et al., 1986; Evans et al., 1993; Jacquim-Gadda et al., 1997; Lyketsos et al., 1999), there was no effect of education on cognitive change (Hultsch et al., 1998; Carmelli et al., 1997), there was an effect of education, but only in a sub-group (Colsher et al., 1991; Farmer et al., 1995; Butler et al., 1996; Schmand et al., 1997) and a group where there was an effect of education, but only in certain outcome measures (Schaie, 1989; Arbuckle et al., 1998; Christensen et al., 1997).

When discussing the relationship of education to cognitive impairment and dementia Gilleard (1997) cited two UK papers (Brayne and Galloway, 1990; O'Connor et al.,

1989) that offered insight into the conflicting results in the published literature. Both these papers showed a link between fewer years of education and worse performance on cognitive tests, in this case mental status questionnaires (such as the MMSE). However, they failed to show a link between clinically diagnosed dementia and education. Thus, less education may make the diagnosis of dementia more likely where the diagnostic process relies heavily on tests of cognition but this link is much less evident when the diagnosis is based around clinical features. This finding is reinforced by Anstey & Christensen (2000) who found that education was protective against cognitive decline in each of 7 papers they reviewed where cognitive decline was measured using a mental status instrument. The apparent 'protection' against cognitive decline conferred by education may in fact simply be an association with the ability to perform psychometric tests, in other words the continuity of trait intelligence. Screening cases for dementia using mental status instruments may lead to a potential bias acting in opposite directions in people of differing mental ability – it may lead to an underestimate of risk of dementia in more highly educated people (Ott et al., 1999).

Pathological studies would be important in identifying a definite link between educational level and risk of dementia, both VaD and AD. Del Ser et al. (1999) used data from the Dementia Study Project of the University of Western Ontario (Merskey et al., 1985). This was a prospective clinico-pathological study from a tertiary memory clinic. During the period 1986-1993, autopsies were carried out on 95 participants who had died. The focus of this study was on Lewy body dementia and AD: cases who did not have either of these diagnoses were excluded (n=6) and educational data were available in 87 individuals (38 men, 49 women). All had dementia diagnosed according to DSM-III criteria. Educational level was categorised as below high school, high school and above high school.

This study showed some interesting results. Those with less education were significantly older at the time of onset of dementia than the middle and highest groups. The mean age at onset in the lowest group was 71.7 (7.6), in the middle

group was 66.1 (8.2) and in the highest group was 68.1 (7.0), p=0.01. The mean age at death was also lower in the group with more education. There was no difference in the duration of dementia (estimated from time of onset to time of death) between the educational groups. There were significant differences found in the frequency of type of pathological lesions found at autopsy. The authors compared those with neurodegenerative lesions alone to those with neurodegenerative lesions with added vascular lesions. There were more people with neurodegenerative lesions plus vascular lesions in the group with less education. Those with neurodegenerative lesions alone had more years of education (mean 12.0 years, SD 3.4) than those with neurodegenerative lesions plus vascular lesions (mean 10.9 years, SD=3.5), p=0.01 using a Student's t-test.

If less education were a causal risk factor for dementia, then it could be hypothesised that those with less education would have more pathological lesions when compared to individuals with more education. This could lead to several consequences. Firstly we might expect an earlier age at onset in those with less education. This was not the case, and in fact is similar to previous results (Moritz & Pettiti, 1993; Duara et al., 1996). There is no obvious explanation for this. There may be a referral bias; those with greater education (or higher socio-economic status) may be more likely to seek medical help sooner and thus be diagnosed at an earlier stage. Secondly, the age at death in those with dementia might also be expected to be lower in those with less education. Again, this was not the case, supporting data published by Stern et al. (1995), who found an increased risk of death in people with AD who had greater educational attainment. Stern et al. (1995) thought that those with more education would require a greater pathological burden to reach the same level of dementia. This is not borne out by the data presented above by Del Ser et al. (1999) where the volume of pathological burden was not influenced by educational level. However, the pathological correlate of lower educational level seems to be an increased frequency of vascular lesions additive to neurodegenerative lesions. This is supported by data from the Nun Study (Snowdon et al., 1997). This might also explain the

findings of Cobb et al. (1995) where there was a link between lower education and non-AD dementia.

Drawing conclusions about the effect education has on risk of dementia has been made slightly easier by the recent publication of a meta-analysis (Caamaño-Isorna et al., 2006). The authors included 19 studies, 13 cohort studies and 6 case-control. This meta-analysis concluded that low versus high education was associated with increased risk of dementia with relative risk between 1.44 and 1.79. This was the case for dementia, AD and non-AD dementia. When low and medium education was compared to high education, there was still an increased risk of dementia. This paper presented sensitivity analysis. The authors assumed that the data included represented only half of all conducted studies and that the unpublished studies found null associations. Low education remained a risk factor for all dementia (RR=1.27, 95% CI 1.11-1.45). As with any meta-analysis, there are of course limitations to be considered prior to accepting results. Importantly, there was a great deal of heterogeneity in measurement of education. For example, illiterate people were compared to literate in one study, whereas other studies compared "grade school" versus "high school". The varying cultural settings of the study are also marked. It may not be accurate to compare number of years of education in the USA to Southern Europe, for example, as they may represent secularly separate entities.

The balance of evidence would tend to imply that there is indeed a link between lower educational level and higher risk of dementia, but at the moment there is not enough evidence to support the idea of a causal link. However, Caamaño-Isorna et al. (2006) boldly claim that their meta-analysis provides evidence that fulfils Bradford-Hill's criteria of causation for low education and dementia:

Strength of association – incidence of dementia is higher in those with low education

Dose-response relationship – risk of dementia increases as education decreases

Temporality – association is observed in longitudinal studies

Consistency – studies employing differing methodology provide results in similar directions and sensitivity analysis suggest publication bias is minimal

Analogy – similar results in dementia, AD and non-AD dementias

Biological plausibility – results can be explained by cognitive reserve hypothesis

It may be too far a leap to accept the causal nature of low education and dementia. There are problems with completely accepting the biological plausibility of the cognitive reserve hypothesis as the only mechanism linking low education to risk of dementia (this is discussed in greater detail below). It may be for example that large and longitudinal studies may link vascular disease to cognitive decline and risk of dementia. Pathological data would also tend to support this idea, that the excess risk of dementia in those with lower education may be mediated via a vascular mechanism.

The precise mechanisms linking lower educational attainment with dementia are not obvious. It is likely that the concepts of mechanisms underlying this link are similar to mechanisms linking lower childhood mental ability and dementia and are discussed further in the following section.

Possible mechanisms linking childhood mental ability and risk of dementia

Lower mental ability in childhood and early life is associated with a higher risk of dementia in older adults. These factors also appear to be linked to poorer health, greater functional impairment in later life and a higher risk of mortality throughout life (Batty & Deary, 2004). The mechanisms linking these factors are not immediately clear. The link between childhood mental ability and mortality was discussed above. Potential mechanisms involved in this association may also be

important in the link between lower childhood mental ability and dementia, and bear some repeating.

In an editorial looking at emerging associations and plausible mechanisms linking early life intelligence and adult health, Batty & Deary (2004) discussed the possible mechanisms. These include the following:

1. Intelligence is an 'archaeological record of physiological and psychological insults (e.g. illnesses throughout life).
2. Intelligence predicts privileged socio-economic circumstances (e.g. higher educational achievement, better employment status).
3. Intelligence is an 'intrinsic indicator' of "general body integrity" (e.g. as measured by general processing speed).
4. Intelligence is a marker of stress coping mechanisms (higher intelligence allows both stress-situational avoidance and improved coping when higher stress environments are encountered).
5. Intelligence may determine health behaviours (e.g. smoking, physical activity, diet).

Any, all or some of the above may provide the actual link between health and intelligence. Indeed, different mechanisms may operate at different times in a person's life.

The potential mechanisms listed above are described by the authors as "non-exclusive". They do not relate specifically to dementia. Empirical testing of possible mechanisms specific to dementia is required to shed further light.

It has been suggested that lifestyle differences such as smoking, nutrition, alcohol, and occupation may provide an important link. Whalley et al. (2000) concluded that "Childhood mental ability may.....shape adult health-related behaviors, some of which could predispose to late-life cognitive decline and dementia." (Whalley et al., 2000, p. 1458). The suggested links include lower socio-economic status, which is linked to both lower mental ability (Evans et al., 1997; Karp et al., 2004; Wilson et al., 2005) and cerebrovascular disease (Starr, 1999). Smoking and poor diet have also been mentioned, possibly linking lower socio-economic status and lower childhood mental ability through an association with vascular disease.

The Nun Study (see above) could be taken as argument against mid-life environmental associations, possibly suggesting a more direct link between lower mental ability in early life and dementia. Whilst the relative homogeneity of the participants could limit the generalisability of the results, it also provides an interesting insight into mechanisms. The nuns were all female, shared many lifestyle experiences (including housing, occupation, socio-economic status, smoking, alcohol, social support networks) and shared similar access to medical care. This could suggest "sisters with low linguistic ability in early life brought risk factors with them when they joined the religious congregation at an early age" (Riley et al., 2005, p. 346). As with many putative epidemiological associations, it remains very difficult to draw firm conclusions on directions of action and causality between associated epidemiological phenomena.

The homogeneity of the participants in the Nun Study has prompted further debate. Rabbitt et al. (2003) postulate that the very demographic and health factors shared among the nuns has a biasing effect. Socio-economic status, linked to better nutrition, higher birth weight and better health in infancy, may be involved in the absolute level of early adult mental ability (Osler et al., 2003; Richards et al., 2001; Shenkin et al., 2001). In addition to an effect on peak mental ability, demographic factors in very early childhood factors may have an influence on maintenance of intellectual vitality and/or prevention of cognitive decline. Rabbitt et al. (2003)

conclude that these shared socio-economic factors "may have determined the nuns' futures long before they wrote their autobiographical notes" (Rabbitt et al., 2003, p. 64).

A slightly different way of looking at mechanisms is that higher mental ability may be protective against cognitive decline and dementia. Whalley et al. (2000) suggested that the presence of a higher mental ability in childhood allowed better access to health information thus presenting better opportunity to make advantageous lifestyle choices. Once again, socio-economic status seems of vital importance, perhaps in reducing exposure to 'environmental factors'.

The possibility must be considered that lower early life mental ability represents a very early manifestation of AD. It is almost unthinkable, however, that the pathological processes which eventually lead to AD are present in the brains of children as young as 11. Nevertheless, Riley et al. (2005, p. 346) said of the link between lower mental ability in early adult life and dementia in later life that the "question……remains to be answered whether neuropathological changes were already operating in early life, resulting in low…..scores in participants, or whether the linguistic ability measure simply marks those who are susceptible to the development of Alzheimer's disease pathology later in life".

Snowdon et al. (1996) presented another possibility as to a possible mechanism linking early life mental ability and late-life cognitive status: namely, the 'brain reserve hypothesis', which is discussed below. The authors rather confusingly state "Sisters with low linguistic ability in early life may have had less neurocognitive reserve capacity when they entered the convent. This reduced reserve capacity may have made them more vulnerable later in life to the consequences of the neuropathology of Alzheimer's disease. This was our hypothesis prior to analyzing the data. That is, we expected that high linguistic ability (a potential indicator of brain reserve) would prevent those with abundant neurofibrillary tangles and senile plaques of Alzheimer's disease from expressing the symptoms of the disease"

(Snowdon et al., 1996, p. 531). This statement reflects a major difficulty in trying to accurately identify mechanisms involved in the association between lower early life mental ability and cognitive decline: there is a lack of clarity definition. Does lower childhood mental ability predispose to cognitive decline or does higher ability protect against it? Or indeed is there a separate as yet unidentified link between mental ability in early life and cognitive status in later life? The theory that health benefits accrued by having higher intelligence in early life leads to a protection against cognitive decline seems plausible. It has though been pointed out that there may be other equally plausible mechanisms. For example, cognitive processes may directly cause socio-economic or health advantages (Gottfredson & Deary, 2004).

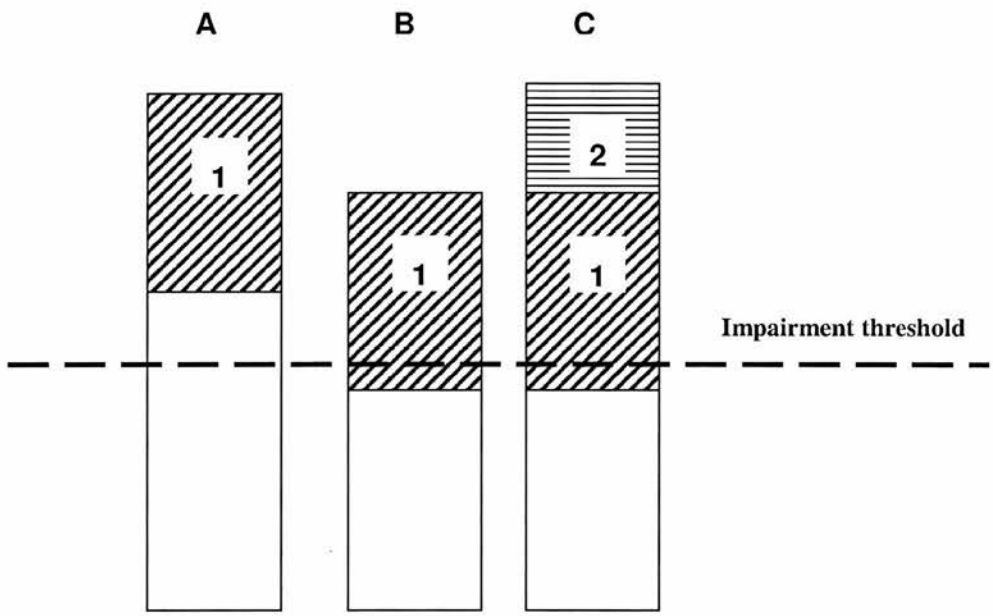
The brain reserve hypothesis

The concept of brain reserve, or a threshold factor, in dementia has been around for a long time. The large post-mortem pathological studies in dementia (Roth, Tomlinson & Blessed, 1966; Roth, Tomlinson & Blessed, 1967; Blessed Tomlinson & Roth, 1968) showed many instances in individuals where the presence of AD pathology did not always correlate with the clinical manifestation of dementia. Satz (1993, p. 274) was prompted to conclude that "These studies provided the first evidence for the threshold and reserve concepts in dementia and raised implicitly the possibility of individual differences in reserve capacity".

The crux of the threshold model of dementia is that individuals only exhibit dementia when cognitive or neurological reserve capacity falls below a specific threshold. Individuals may be 'buffered' from the consequences of dementia and cognitive decline by having greater 'neurocognitive' or 'brain' reserve, or be more predisposed to cognitive decline by having lower cognitive reserve.

The cognitive reserve hypothesis is easier to understand when represented in diagrammatic form, shown in figure 1.4. This shows three hypothetical situations.

Figure 1.4: Diagrammatic representation of the brain reserve hypothesis



In figure 1.4, the 'impairment threshold' represents the point at which symptoms become evident thus allowing a diagnosis of disease to be made. The area above the line therefore represents the 'brain reserve'. The core of this theory holds that where there is greater reserve, a neuropathological lesion may not result in enough decline to cause symptoms. This is represented by individual 'A' above. This compares to individual 'B' where a similar neuropathological lesion results in symptoms because there is less reserve and so the functional impairment threshold is crossed. Another aspect to this hypothesis is demonstrated in individual 'C'. Here, the summative effect of multiple lesions causes symptoms; neither lesion 1 nor 2 is enough on their own to cause dementia. There are further nuances to this theory, which I will not

dwell on. In short, it is suggested that temporal factors may operate and lesions may only cause symptoms in the presence of specific challenging factors.

The above theory of brain reserve, as reviewed most elegantly by Satz (1993) is essentially a passive model. In other words, there is a fixed threshold for the development of impaired cognition. Stern (2002) argues that this model does not take into account potential individual differences in how the brain is affected by specific pathology (e.g. individuals A and B may have different cognitive response to the exact same pathological insult) and also does not account for the possibility that different pathologies may cause qualitative differences in cognitive processes.

Stern (2002) proposed that brain reserve is an active process to compensate for brain damage and that it can take two forms. The first model is cognitive reserve, whereby the brain uses additional synapses or redundant neural networks in the face of pathological insult. In this model, having a higher cognitive reserve implies that the brain is more cognitively efficient. The second model is compensation where alternative brain structures (not normally used in the intact brain) are used to achieve the same cognitive goal.

An analogy here might aid the distinction between the passive and active models of brain reserve. The passive model can be thought of like an oil reserve – there is a larger store of this particular resource held back, which may be drawn upon when required. The active models can be thought of like a sporting team reserve – there are resources held in readiness, the deployment of which varies with the specific task required of that reserve in any given situation.

There may be some evidence from functional brain imaging task-related activation studies to support a cognitive reserve as defined above. The evidence remains slightly conflicting in terms of definition of reserve. Brains of people with AD have been shown to have more extensive activation when compared to controls (Becker et al., 1996; Grady et al., 1993; Backman et al., 1999). These findings are interpreted as

compensation, that patients with AD achieve a certain task by recruiting alternative brain areas. This theory has been challenged; it has been suggested that the varying appearance on brain imaging is caused by the fact that the tasks are simply cognitively more difficult for those with AD (Herbster et al., 1996). Stern et al. (2000) performed a functional positron emission tomography (PET) scan trying to control for the difficulty of the cognitive task. They identified a brain area activated by a verbal recognition task, and showed that in health (n=11) this area activated more as task difficulty increased. Only 3 out of 14 patients with AD activated the same brain area as the healthy controls. This implies that those with AD activated a different neural network in response to an effortful cognitive task. The authors interpreted this as evidence for compensation due to varying levels of cognitive reserve in people with AD.

There is evidence from neuroimaging that cognitive reserve is related to years of education. Stern et al. (1992) looked at regional cerebral blood flow in people with probable AD, taking a deficit of perfusion in the parietotemporal region as a broad marker of severity. When they compared people of similar levels of severity of dementia, they found that there was a greater perfusion deficit in those with more years of education. This finding can be explained if those with more education have more cognitive reserve and thus it takes a greater amount of pathology to cause the same severity of clinical disease.

There are several problems with the brain reserve hypothesis – whether active or passive. Most importantly, the entire theory must be regarded as a hypothetical construct. This remains so "because of difficulties, largely historical, in defining and measuring the term brain reserve, particularly as it relates to the threshold concept, [and] little research has been published directly on this topic." (Satz, 1993, p. 274). The "largely historical" problems with definition and measurement have not changed since the publication of Satz's seminal paper (in 1993), and remain a very pertinent issue. For example, people have used all of brain size, critical volume of functional brain tissue, sensory evoked potentials, EEG findings and more recently

neuroimaging findings as a measure or a marker of brain reserve (Schafer, 1982; Katzman, 1993; Staff et al., 2004). There are more problems with definition of brain reserve. Katzman (1993) holds that density of neocortical synapses related to cognitive change in AD, with education increasing brain reserve by increasing synaptic density. However, data explicitly linking synapses to behaviour are lacking (Coltheart, 2004). Stern (2003, p. 451) states "presumably, the physiologic variability subsumed by cognitive reserve is at the level of variability in synaptic organization.....Thus cognitive reserve implies anatomic variability at the level of brain networks, while brain reserve implies differences in the quantity of available neural substrate." The lack of clarity of defining features is a major problem with the brain reserve hypothesis, as is a lack of hard data in the definition of "brain networks" and "available neural substrate".

Proving that people with AD activate different brain areas in response to a cognitive challenge does not prove the existence of cognitive reserve. There may be a direct effect of AD on the brain causing differential activation rather than any observed effect being mediated by differing levels of cognitive reserve.

There is a very important argument at the heart of brain reserve capacity theory: namely, does having greater reserve offer up innate protection against falling below the impairment threshold, or does having less reserve cause an innate predisposition to developing symptoms? This very circular argument may not have a single answer. Indeed, the argument could go yet further, that brain reserve is dynamic and may be different at differing times in life. For example, mental stimulation may improve cognitive function even in patients with dementia (Breuil et al., 1994; Koh et al., 1994). However, it is not clear if this operates at a 'neural network' or synaptic level, or whether it may influence psychological behaviour such as improving coping strategies and/or problem solving to therefore minimise the effects of cognitive decline on day-to-day activities.

These major difficulties must therefore pose a grave concern in accepting the presence of any entity that physically represents a reserve capacity. The apparent reserve may simply represent a tendency of medical diagnosis to require a threshold. This may not in fact be the case for dementia, especially given recent work on mild cognitive impairment implying that cognitive deficits may predate the diagnosis of dementia by years (Petersen et al., 1999; Winblad et al., 2004; Petersen & Morris, 2005). The dementia threshold then does not necessarily derive from a pathophysiological or anatomical basis, but rather could reflect the clinical features and neuropsychological tests required to make the diagnosis. An example in routine medical practice is the MMSE. It is commonly held even in major research undertakings that a score of 24 or under is representative of dementia, or cognitive impairment. This threshold is arbitrary and not wholly accurate – all individuals of scores of 25 are not cognitively intact, and people may score 30 and yet be significantly demented; scores can vary from day to day with other factors such as physical illness, so a person may score 23 one day and 26 the next.

Stern (2002, p. 448) argued that "the concept of reserve should be extended to encompass variation in healthy individuals' performance, particularly when they must perform at their maximum capacity." Again this point highlights one of the main difficulties of the cognitive reserve hypothesis. The label of cognitive reserve may simply be a function of the individual differences in ability to cope with the cognitive deficits of dementia.

Having a true measure of mental ability in childhood allows a life course approach to studying cognitive ageing and cognitive reserve hypotheses, which might shed more light on this as yet unresolved concept (Richards & Deary, 2005).

The role of childhood mental ability in 'normal' cognitive ageing: implications for risk of dementia

It is important to briefly discuss the concept of childhood mental ability and its relation to 'normal' cognitive ageing: some people consider cognitive ageing and dementia to be part of a spectrum of cognitive decline. Therefore if childhood mental ability is associated with cognitive ageing then it may also be associated with dementia. There are also some basic concepts of individual differences in mental ability which need to be discussed, albeit briefly.

It is perhaps inherent in the definition of cognitive ageing that decline in cognitive function is an inevitable consequence of ageing. For example, Whalley et al. (2004, p. 370) state "The term cognitive aging describes a pattern of mild age-related impairments in cognitive functions". For some cognitive abilities, such as reasoning and mental speed (i.e. fluid intelligence), this pattern of decline would appear to be true. However, these declines represent mean declines in the population measured (Deary, 2000). Individual differences mean that, for some individuals, cognitive abilities might improve with age (Deary, 2000; Wilson et al., 2002). For other individuals, especially those with dementia, the decline in cognitive ability is extremely rapid and has a catastrophic effect on their ability to carry out everyday tasks.

Childhood mental ability is an important determinant of cognitive ageing. Deary et al. (2000) were able to show that approximately 50% of the variance of general intelligence measured in people aged in their late seventies was explained by a score of mental ability measured at age 11. This then could represent a baseline of general mental ability which remains throughout life. The NIA Aging and Genetic Epidemiology Working Group (2000) recommend that there is a distinction made between baseline cognitive ability and rate of cognitive change associated with ageing. There are likely to be factors that lead to individual differences in rate of decline in cognitive function, the most important of which is the probably the presence of disease (e.g. dementia and cerebrovascular disease). Other factors

affecting rate of cognitive decline may be specific factors directly leading to worse neural function (Whalley et al., 2004). These factors may not be disease related and may be cognitive processes. For example, impaired executive function (Salthouse et al., 2003) and slowed mental speed (Salthouse, 1996) have both been proposed to be important mediators of cognitive ageing.

Longitudinal studies are required to study individual differences in rates of change of cognitive ageing (Schaie & Hofer, 2001) and are useful to confirm results from cross-sectional data. Anstey & Christensen (2000) reviewed 34 longitudinal studies of cognitive change with 'normal' ageing. Their review specifically aimed to identify factors associated with cognitive decline. As part of their conclusion, they state "An important finding, not captured within the data presented.....was that large numbers of older persons did not decline over the follow-up period." (Anstey & Christensen, 2000, p. 174). The reason thought to be most important in this preservation of cognitive function was a continuing period free of ill-health (Schaie, 1996).

There are implications for this thesis to be taken from the associations between childhood mental ability and 'normal' cognitive ageing. Most importantly, factors which are associated with cognitive decline may also be linked to increased risk of dementia. Thus in chapter IV, impairment in cognition is demonstrated in healthy volunteers with changes on the resting electrocardiograph. This may have some link to mechanisms of dementia in people with lower childhood mental ability.

Conclusion

This introductory chapter began by defining dementia and its sub-types. The role of environmental and other risk factors for dementia were discussed. Diagnostic uncertainties and overlap between the types of dementia were highlighted, aiming to possibly shed light on vascular factors and their association with causes of dementia.

The second part of this chapter aimed to describe the methodology of the SMS1932 and its follow up studies. This chapter helps to put into perspective the importance of childhood mental ability, which may act as a base-line measure of mental ability. This then allows cognitive decline to be measured and factors leading to cognitive decline to be specifically tested. The SMS1932 has allowed crucial research in the field of cognitive ageing. The follow up studies of the SMS1932 demonstrate that childhood mental ability is associated with longevity and mortality, which may have some relevance when discussing possible mechanisms of action for a link between lower mental ability in early life and risk of later cognitive decline.

In part 3 of this chapter, I reviewed literature linking early life mental ability and late life dementia. The results of this are not conclusive, but seem to suggest that there is a higher risk of dementia in those with lower mental ability in childhood. Lower educational level would also seem to be associated with an increased risk of dementia. Published data might suggest that the excess risk of dementia is mediated through vascular mechanisms, and some postulated mechanisms as to how this link might occur were discussed with particular reference to the cognitive reserve theory. The concept of individual differences in cognitive performance and cognitive decline was raised, emphasising that these individual differences must be taken into account both for clinical practice and in research.

This thesis will now go on to describe original research adding to literature studying the association of childhood mental ability to the risk of dementia in later life.

I will specifically test the following hypotheses:

1. Lower mental ability in childhood increases the likelihood of dementia in old age.
2. The effect of lower mental ability on increased risk of dementia is on dementia per se rather than being specific to either AD or VaD as sub-types of dementia.

3. Diagnosing dementia requires evidence of decline from a prior cognitive status. I test the hypothesis that using an estimate of pre-morbid intelligence as a diagnostic tool remains valid even in individuals with mild-moderate dementia.
4. In attempting to examine possible mechanisms linking childhood mental ability to late-onset dementia, I test the hypothesis that vascular risk factors (as identified by ECG changes) are associated with impaired cognition in elderly people.

Chapter II: Case-control study of childhood mental ability and late-onset dementia

This chapter aims to test the hypothesis that lower mental ability in childhood is associated with increased risk of dementia in later life. A further aim was to assess if any effect was general to dementia *per se* or specifically related to either AD or VaD sub-types of dementia. The aims are achieved by describing a case-control study investigating the impact of childhood mental ability on the risk of late-life dementia. All cases and controls were born in 1921 and had participated in the SMS1932.

Methodology

Cases

A case was defined as someone who had had a diagnosis of dementia made after the age of 65 who had taken part in the SMS 1932 and who could be identified on the register of births, deaths and marriages for Scotland. ICD criteria were used in the definition of dementia. The cases for this study were identified from 3 sources – from patients attending the Lothian Memory Treatment Centre (LMTC), from the Royal Victoria Hospital case register, and from the Royal Edinburgh Hospital (REH) Dementia Case Register. A total of 300 potential late onset dementia cases born in 1921 were identified, but one of these did not have dementia and two others had pre-senile dementia. Specific details on case identification are discussed below.

Lothian memory treatment centre

The Lothian Memory Treatment Centre (LMTC) was opened in 1999. It functioned as a tertiary referral centre taking referrals from hospital consultants, mainly old age psychiatrists but also geriatricians and general physicians. Its aim was not to manage

the spectrum of dementia illness in the community, but rather to facilitate a rational approach to the introduction of acetyl-cholinesterase inhibitors. Patients commenced on these then novel drugs were monitored very carefully. Diagnosis was made at clinical interview, backed up by neuropsychological assessment. The full range of laboratory investigations were available to the clinic as was the use of CT, MRI and PET scans, serially where indicated. The diagnosis of dementia and sub-type of dementia was made on a clinical basis.

A minimum dataset was recorded for every individual. This included maiden names for women.

The LMTC had a single clinical neuropsychologist (supported by a psychology assistant). Neuropsychological investigation was tailored to the individual but included MMSE and NART in addition to many other tests of cognitive function.

By its nature, the LMTC was designed to monitor the use of new acetyl-cholinesterase inhibitors. This had two major effects. It attracted mainly patients who were suitable for the treatment. In other words they tended to be fit, otherwise healthy people with dementia at the milder end of the spectrum. They also, by definition, had to be living in the community. Recalling the indications for the use of donepezil (the first acetyl-cholinesterase inhibitor introduced for the treatment of dementia), it was intended for use only in patients with AD. In other words the patients who were referred to this tertiary centre almost all had AD, as the majority of patients with other types of dementia (including VaD) had been filtered out at review by a consultant psychiatrist. The introduction of anti-dementia drugs was very newsworthy. This led to another interesting feature about the case-mix of the LMTC; namely, people who knew of the drugs and asked for referral were the ones who were actually referred.

Using patients from this setting as cases in research has strengths and weaknesses, and is of some importance to the way that results of the thesis can be interpreted.

The patients attending the LMTC cannot be considered to be typical of all patients with dementia. They had a limited range of diagnoses, a reduced spectrum of disease severity and tended to come from similar social backgrounds which were often more privileged. Thus, the generalisability of results may be an issue. On the plus side, the patients received an excellent diagnostic work-up leading to a high degree of certainty as to the precise diagnostic category. In addition, neuropsychological assessment that can be compared from patient to patient as the same techniques were employed by a single psychologist.

An issue with a study such as this is the completeness of case identification. If many are missed, this will introduce selection bias into the results. To ensure that all of the people born in 1921 were identified, a thorough search strategy was used. An electronic database of all patients attending the LMTC was available. This covered the period up until November 2001. This electronic database was searched to identify all those born in 1921. Paper records were also scrutinised to identify people who were no longer attending, who were no longer on pharmacological therapy and who had been referred but never assessed in the LMTC. The LMTC kept an up-to date record of patients held on a waiting list. From April 2002 until August 2003, all new patients born in 1921 reviewed in the clinic were identified. Thus the identification of people born in 1921 attending the LMTC can be considered accurate and complete.

REH and RVH dementia case registers

The Royal Edinburgh Hospital (REH) is the main psychiatric hospital, treating adult patients with psychiatric disease for the whole of Edinburgh. It maintains a dementia case-register. Ethical approval was gained to access this register. The clinical coding department of the REH supplied information up to March 2003 for every person born in 1921 who had been treated at the hospital who had a diagnosis of dementia. The information supplied included name, maiden name for women, DOB and diagnosis. The case register covered many years including people who had died years before

and people with early-onset dementia. The diagnostic criteria covered ICD-9 and ICD-10 and came from various consultants. An advantage of using this group of patients as cases in research was that they are a heterogeneous group, representative of people that age who have dementia. They span the spectrum of disease severity and diagnosis; they include in-patients, out-patients and people in residential care; and they come from all social backgrounds in Edinburgh. A disadvantage of using this group is that there is less diagnostic certainty; they came from many different clinical teams and from a longer time period.

The Royal Victoria Hospital (RVH) is a specific geriatrics hospital. An out-reach clinic from the LMTC operated within the RVH. In addition, there was a medical clinic where the consultant physician had an interest in memory disorders, and indeed was a consultant in the LMTC. Further cases of people who had taken part in the SMS1932 were identified from this consultant's general clinic. Their work-up was similar to that in the LMTC.

No case notes were scrutinised for the people on the REH dementia case register. The formal disease coding used by the NHS was taken as the definitive diagnosis. Although it is difficult to ascertain the accuracy of these diagnoses, they must be trusted: all diagnoses were made in specialist secondary care. Audits have shown that diagnoses of dementia may go unrecognised (Harwood et al., 1997; Ardern et al., 1993); however, these have been in acute medical practice not in specialist psychiatric care. It is also difficult to assess the completeness of case finding. It is possible that there were people with dementia treated in the REH who had alternative primary diagnoses and dementia was not coded as it was secondary.

A note on the technique employed to identify population data

For cases and controls, it was essential to be able to match the individual to the information held on the SMS1932 database. This presented several problems. The major problem was matching married women to records from 1932 – often the

woman's maiden name, an essential piece of information, was missing. For cases from the LMTC, maiden names were recorded as part of the minimum dataset. For women from the REH and RVH case registers this was more problematical. It was not insurmountable due to the fact that Register House also holds data on the register of deaths and the register of marriages, organised by year of the event. For example, it is possible to search for all marriages in Scotland of people with a particular surname for any given year. Knowing the woman's first name, date of birth and married surname, it was possible to search through the register of marriages. This was difficult where the first name and second name are in common usage (eg 'Elizabeth' and 'Smith'). Where there was an uncommon forename or surname, the search was more likely to be successful (e.g. 'Greta' and 'McGurn'). Entries on the marriage register include parents' names. These can then be used to confirm whether or not it is the same person on the birth register. A further degree of certainty was added if the birth region matched the marriage region, although this is clearly very variable. The register of deaths contains details on the date, time and place of death. It also details the names and occupation of the dead person's parents, which could be used to help identify that individual on the register of births.

Controls

Cases used in this study were matched to population controls. Cases were matched to two control groups:

> **Control group 1**: matched on age, sex and district of birth registration
> **Control group 2**: matched on age, sex, district of birth registration and father's occupation

Two control groups were used to increase power and also to control adequately for broad parental occupation category.

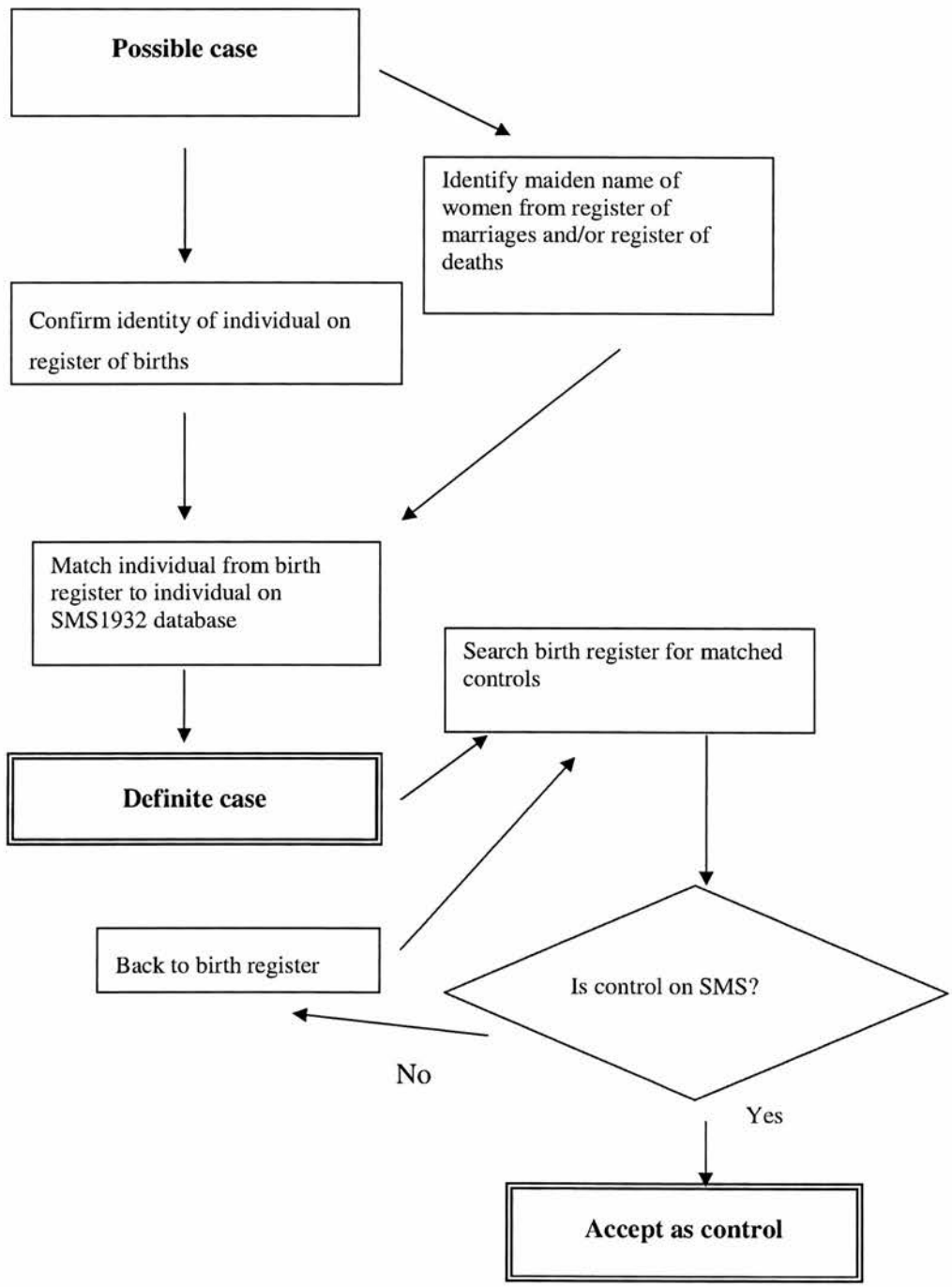
Each case was identified on the register of births held at register house, Edinburgh. For each control group there were two individuals identified as controls. Control group 1 was made up of the person closest before and closest after the case on the register of births who had taken part in the SMS1932. Control group 2 was made up of person closest before and closest after the case on the register of births who shared the same broad parental occupation and who had taken part in the SMS1932. For some people who were born in smaller regions, it was not possible to match controls on paternal occupation.

It is important to note that frequently those in control group 1 were the same as those in control group 2. Therefore it is not statistically accurate to compare the mean MHT in the two control groups.

Cases and controls used in this study

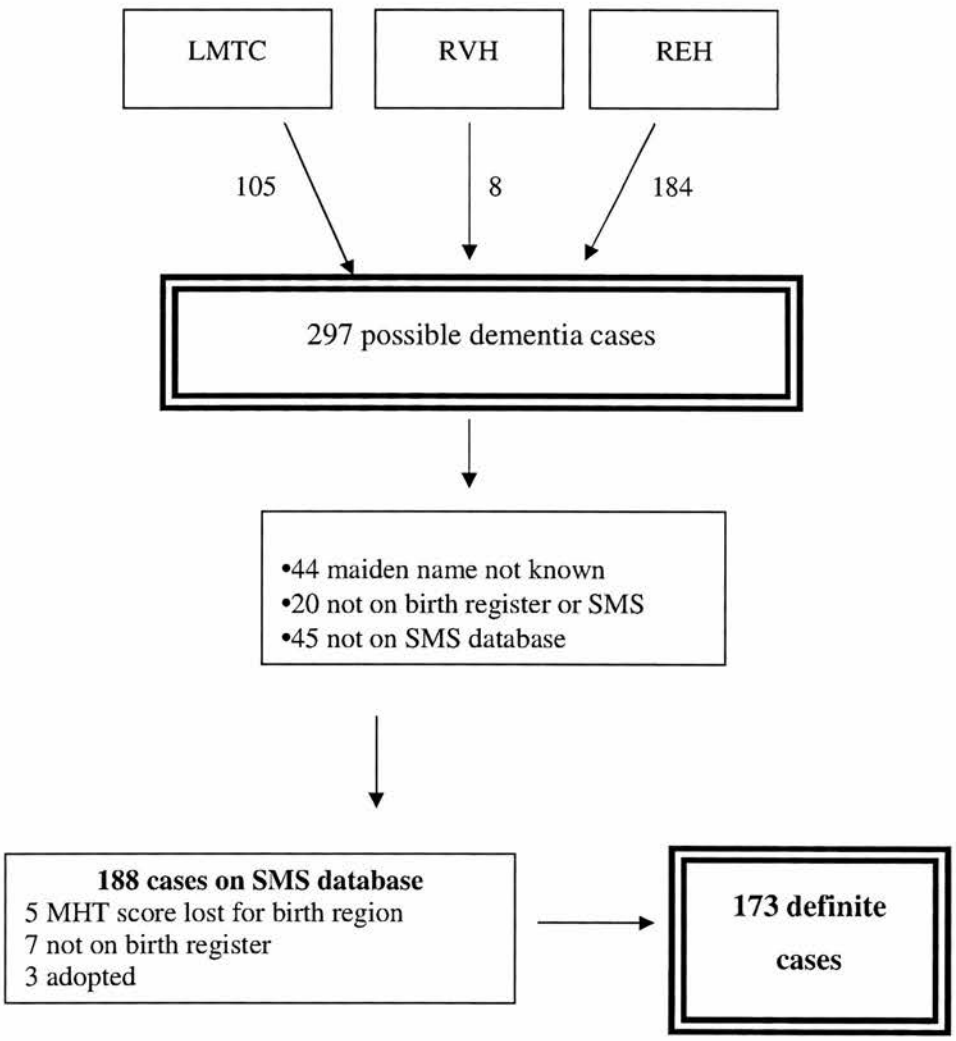
The methods used in matching cases to population controls is probably best summarised as a flowchart, figure 2.2.

Figure 2.2: Matching of cases to population controls using data from the register of births, deaths and marriages



Using the methods shown in figure 2.1 eventually yielded 173 cases. Figure 2.2 shows a flow diagram of how this figure was arrived at.

Figure 2.2: Flow-chart depicting case identification



Of the 297 cases with late onset dementia there are 44 females whose maiden name is not known; therefore these cases were not able to be matched to either the Scottish Mental Survey for 1932 (SMS) or the birth register. Another 20 cases have not been

matched to either the SMS or the birth register. There are 45 cases that have been matched to the birth register but not to the SMS. This leaves the remaining 188 cases who were matched to the SMS database. Of these, there are seven that have not been matched to the birth register. Three have been matched to the birth register but were adopted, and so were excluded as no data were known about paternal occupation. Five have been matched to the birth register but the SMS records have been lost for their birth registration district. This leaves a total of 173 definite cases.

Demographic information recorded for cases and controls

Paternal occupation was used as a proxy measure of social class. For social class, occupations were coded using the Registrar General's Classification, obtained from the 1951 Census Classification of Occupations (HMSO, 1956). This divides occupations into five categories:

I	Professional e.g. lawyer, doctor, clergyman, professional engineer
II	Intermediate e.g. proprietor of business, trained nurse, artist
III	Skilled e.g. clerk, policeman, miner, chauffeur
IV	Partly skilled e.g. fisherman, carter, stoker, conductor
V	Unskilled e.g. labourer, railwayman, watchman

More recent classifications of occupations have split group III into III(N) for non-manual workers and III(M) for manual workers.

Other demographic information recorded was the age of the father at the birth of the child, the age of the mother at the birth of the child and the duration of the parents' marriage at the birth of the child. All of this data is recorded on the register of births deaths and marriages.

Statistical analyses

Descriptive statistics are presented as mean and standard deviation except where stated. Differences in means were calculated using a t-test and ANOVA. Univariate ANOVA, calculated using general linear modelling, gives the relationship between MHT and diagnosis of dementia in cases and controls. Because this is a matched case-control study, odds ratios (OR) for the likelihood of having a diagnosis of dementia are calculated using conditional logistic regression. Covariates entered into the conditional logistic regression model were maternal age at birth of subject, paternal age at birth of subject, length of time parents had been married at birth of subject and paternal occupational category. The rationale for choosing these variables as covariates was two-fold. Firstly, they were measurable as the demographic information is held on the national register of births. Secondly, other than socio-economic status, there is no great wealth of data to draw on as to precise determinants of IQ in childhood (Richards & Wadsworth, 2004) that may therefore act as confounders in this study. It could be postulated that the covariates used above may be markers of early adverse circumstances and thus have an effect on MHT score aged 11.

Sample size

Sample size can be estimated from data presented from the ABC1921 (Whalley et al., 2000). The mean MHT for survivors free of dementia in 1997 was 36.2 (95% CI 35.1-37.3). Using these figures gives a calculation of the standard deviation at 13.2. Dementia cases had a mean MHT score of 29.6, with a calculated standard deviation of 15.5. This is 0.5 of a standard deviation lower. Using the 1997 figures, 80 cases versus 80 controls provides 82.6% power at α=0.05.

Results

Descriptive statistics

The mean MHT scores for cases and controls are given in table 2.1.

Table 2.1: Mean MHT scores for cases and controls

Group	n	mean MHT (SD)	Sig.
Cases	173	38.3 (14.6)	
Control group 1	346	38.8 (14.5)	p=0.67
Control group 2	328	37.5 (14.2)	p=0.56

Overall, there is no significant difference in MHT scores in cases and controls.

The mean MHT for cases and controls for the five broad paternal occupational classes are shown in table 2.2.

Table 2.2: Mean MHT scores for cases and controls by paternal occupational group

Paternal occupation group	Case/control	n	mean MHT (SD)	Sig
I	Case	5	58.2 (5.6)	
	Control group 1	5	51.8 (12.1)	p=0.31
	Control group 2	3	50.3 (4.0)	p=0.08
II	Case	15	43.9 (12.6)	
	Control group 1	33	45.3 (13.1)	p=0.74
	Control group 2	27	40.2 (16.0)	p=0.44
III	Case	102	37.4 (14.8)	
	Control group 1	209	38.7 (13.8)	p=0.45
	Control group 2	204	39.0 (13.9)	p=0.35
IV	Case	30	36.8 (14.0)	
	Control group 1	47	39.5 (14.3)	p=0.42
	Control group 2	60	33.4 (13.5)	p=0.27
V	Case	18	37.4 (14.2)	
	Control group 1	38	32.3 (14.5)	p=0.22
	Control group 2	34	32.1 (13.1)	p=0.19

There are no significant differences in MHT score between cases and controls in any of the five broad paternal occupational classes.

The effect of socio-economic status is examined in table 2.3 where the mean MHT scores for each of the paternal occupational groups is shown in cases and controls. Within-group differences were analysed using ANOVA, with MHT score entered as the dependent variable and occupational group as the co-factor. There is a clear effect of socio-economic status in cases and controls. As expected there is a decline in MHT as the socio-economic classification goes from I to V and those in higher

socio-economic groups on average have higher MHT scores. This effect is similar in cases and in both control groups.

Table 2.3: The effect of socio-economic status on MHT scores in cases and controls

Occupational group		n	mean MHT (SD)	F	Sig.
Cases	I	5	58.2 (5.6)		
	II	15	43.9 (12.6)		
	III	102	37.4 (14.8)		
	IV	30	36.8 (14.0)		
	V	18	37.4 (14.2)		
	Unknown	3	25.3 (6.4)	3.85	p=0.011
Control group 1	I	5	51.8 (12.1)		
	II	33	45.3 (13.1)		
	III	209	38.7 (13.8)		
	IV	47	39.5 (14.3)		
	V	38	32.3 (14.5)		
	Unknown	14	36.3 (20.6)	3.94	p=0.002
Control group 2	I	3	50.3 (4.0)		
	II	27	40.2 (16.0)		
	III	204	39.4 (13.9)		
	IV	60	33.4 (13.5)		
	V	34	32.1 (13.1)	4.6	p=0.003

The frequencies of types of dementia in cases are shown in table 2.4.

Table 2.4: Frequencies of types of dementia in cases

Type of dementia	n	%
AD	86	49.7%
VaD	32	18.5%
Mixed	8	4.6%
Dementia (unspecified)	44	25.4%
Parkinson's disease	2	1.2%
'Other neurodegenerative'	1	0.6%

AD was the most frequent type of dementia. There were a small number with dementia associated with Parkinson's disease. There were a large group who had unspecified dementia as their primary diagnosis. This term comes from an ICD-9 code. It was used where there was not enough information to determine the exact cause for dementia, especially where there was thought to be a mixed picture but where the underlying aetiology was less obvious and more difficult to categorise. It is likely that this group contained within it a wide spectrum of diagnoses, including for example alcohol related dementia and Lewy-Body dementia. There were eight cases with 'mixed' dementia where there was a clear identifiable vascular component to their dementia. These cases were therefore analysed together with the cases with 'pure' vascular dementia. The cases of 'other neurodegenerative disorder' and dementia associated with Parkinson's disease were excluded from further analysis.

Different sources of cases might have an important effect on childhood mental ability by introducing a selection bias. The source of the cases, the frequencies of AD, VaD and unspecified dementia are shown in table 2.5.

Table 2.5: Mean MHT scores in different diagnostic groups by source of referral

Type dementia	Source	n	mean MHT (SD)	F	sig.
AD	LMTC	46	40.0 (16.0)		
	REH	37	39.9 (12.7)		
	RVH	3	37.4 (16.8)	0.01	p=0.99
VaD	LMTC	10	38.4 (10.4)		
	REH	28	33.5 (14.3)		
	RVH	2	37.5 (2.1)	0.53	p=0.59
Dementia (unspec.)	LMTC	8	41.3 (16.4)		
	REH	38	40.8 (11.7)		
	RVH	1	35.0	0.16	p=0.85

Overall, there is no effect of source of referral on MHT score. In particular, there does not seem to be a difference in MHT in cases with AD from the three sources of cases. The cases from the REH dementia case register who had VaD seem to have a lower MHT score, though this is not different to the cases with VaD from the LMTC and RVH.

Table 2.6 gives the frequencies of types of dementia as used in further analyses, the demographic data for cases and the mean MHT scores for these groups.

Table 2.6: Demographic data and mean MHT scores in cases in different diagnostic groups

		Type of dementia		
		AD	VaD	Dementia (unspecified)
n		86	40	44
Age at SMS		10.9 (0.29)	10.9 (0.27)	10.9 (0.27)
Female sex		58 (67%)	22 (55%)	22 (50%)
Born Lothian		63 (73%)	31 (78%)	33 (75%)
Maternal age		30.7 (7.0)	30.2 (5.7)	30.6 (6.5)
Paternal age		33.7 (8.2)	32.0 (6.2)	33.0 (7.1)
Years parents married at birth of subject*		3.9 (1.2-10.5)	5.0 (1.2-10.0)	3.5 (1.3-9.5)
Paternal occupational Category	I	2 (2%)	0	3 (7%)
	II	7 (8%)	4 (11%)	4 (9%)
	III	50 (59%)	25 (66%)	24 (55%)
	IV	16 (19%)	6 (18%)	8 (18%)
	V	10 (12%)	3 (18%)	5 (11%)
MHT score		40.0 (14.5)	35.0 (13.1)	38.7 (15.6)

* results presented as median and inter-quartile range

Using ANOVA, there was no effect of diagnosis on MHT score ($F = 1.65$, $p=0.20$). However, using a t-test to compare means, the lower score for those with VaD compared to those with AD was just outside the limit of statistical significance ($t=1.87$, $p=0.06$). There was no difference between AD and unspecified dementia or VaD and unspecified dementia. It must be stressed here that these results are for all the cases. As discussed above, Whalley et al. (2000) identified a major effect of migration on MHT score, with those who had migrated out of Grampian region scoring higher than those who stayed within Grampian.

The effect of migration on MHT is important and the impact this may have on MHT in this study is demonstrated in table 2.7, where the mean MHT scores for cases and controls are shown by birth region.

Table 2.7: MHT scores in cases and controls by birth region

	Cases		Control group 1		Control group 2	
Region	n	MHT (SD)	n	MHT (SD)	n	MHT (SD)
Edinburgh city	102	37.2 (14.2)	204	41.0 (13.8)	204	38.2 (14.1)
W. Lothian	7	34.0 (10.0)	14	33.6 (14.1)	12	36.7 (14.6)
E. Lothian	8	37.9 (11.4)	16	35.3 (15.6)	12	38.6 (10.7)
Midlothian	13	28.5 (18.9)	26	37.6 (18.3)	26	36.3 (16.4)
Glasgow	7	38.0 (10.9)	14	34.1 (13.8)	14	33.9 (12.6)
Renfrewshire	2	48.5 (16.3)	4	37.0 (17.3)	4	31.3 (18.2)
Lanarkshire	11	39.7 (11.1)	22	34.9 (14.8)	20	35.1 (14.3)
Ayrshire	2	49.0 (12.7)	4	17.5 (12.8)	2	20.0 (16.9)
Roxburgh	3	47.0 (7.2)	6	40.8 (18.6)	4	38.5 (18.1)
Moray	1	55.0	2	49.5 (2.1)	2	49.5 (2.1)
Ross	1	34.0	2	24.0 (2.8)	2	26.5 (0.7)
Dundee	3	29.3 (0.6)	6	39.2 (13.3)	4	45.5 (9.5)
Shetland/Orkney	1	67.0	2	26.5 (21.9)	0	
Perth & Kinross	1	52.0	2	40.0 (28.1)	0	
Inverness	1	59.0	2	26.5 (10.6)	2	33.5 (7.8)
Dumfries	2	59.0 (0.0)	4	38.0 (8.8)	4	49.5 (11.6)
Selkirk	1	37.0	2	28.5 (5.0)	2	18.5 (19.1)
Argyll	1	70.0	2	40.5 (19.1)	2	44.5 (13.4)

Table 2.7 shows some very important data. In most of the birth regions, the cases seem to score higher than the controls, important exceptions being Edinburgh, East Lothian and West Lothian. This implies that there is an effect of migration – those people who have moved regions have a higher childhood mental ability. To explore the effect of migration further, table 2.8 shows the mean MHT scores for cases and controls in those people born in Lothian and those born elsewhere in Scotland.

Table 2.8: Mean MHT in cases and controls, comparing those born in Lothian and elsewhere in Scotland

	Region					
	Lothian		Outside Lothian			
	n	MHT (SD)	n	MHT (SD)	F	sig.
Cases	130	36.2 (14.5)	43	44.6 (13.5)	11.3	p=0.001
Control group 1	260	39.9 (14.5)	86	35.6 (14.0)	5.8	p=0.016
Control group 2	254	38.0 (14.2)	74	35.9 (14.1)	1.2	p=0.27

Tables 2.7 and 2.8 show some very important data. Before interpreting further data it is important to note in summary:

1. All cases came from dementia registers maintained in Edinburgh

2. Cases born in other regions have 'migrated' into Edinburgh. The MHT score is higher in migratory cases born outwith Lothian. This reflects the major association between migration and MHT score.

3. In addition, migrants to Edinburgh (cases) overall have higher childhood IQs than people from their home region (controls).

4. Not all regions have the same average childhood IQ: Edinburgh has the highest mean in Scotland. Controls from within Lothian had a higher MHT score than controls born elsewhere in Scotland.

5. Thus, the childhood IQ of the cases in Edinburgh, but not the controls, is inflated/biased by the high childhood IQ of migrants to Edinburgh – in this instance, controls are more likely to be static and stay in their birth region.

Therefore, if cases are drawn from health registers based upon a background population resident in Edinburgh in old age, given the previous statements, the only valid comparison of childhood IQ is to examine cases and controls who were born in Edinburgh. For this reason, further analyses were conducted only on cases and controls born in Lothian region.

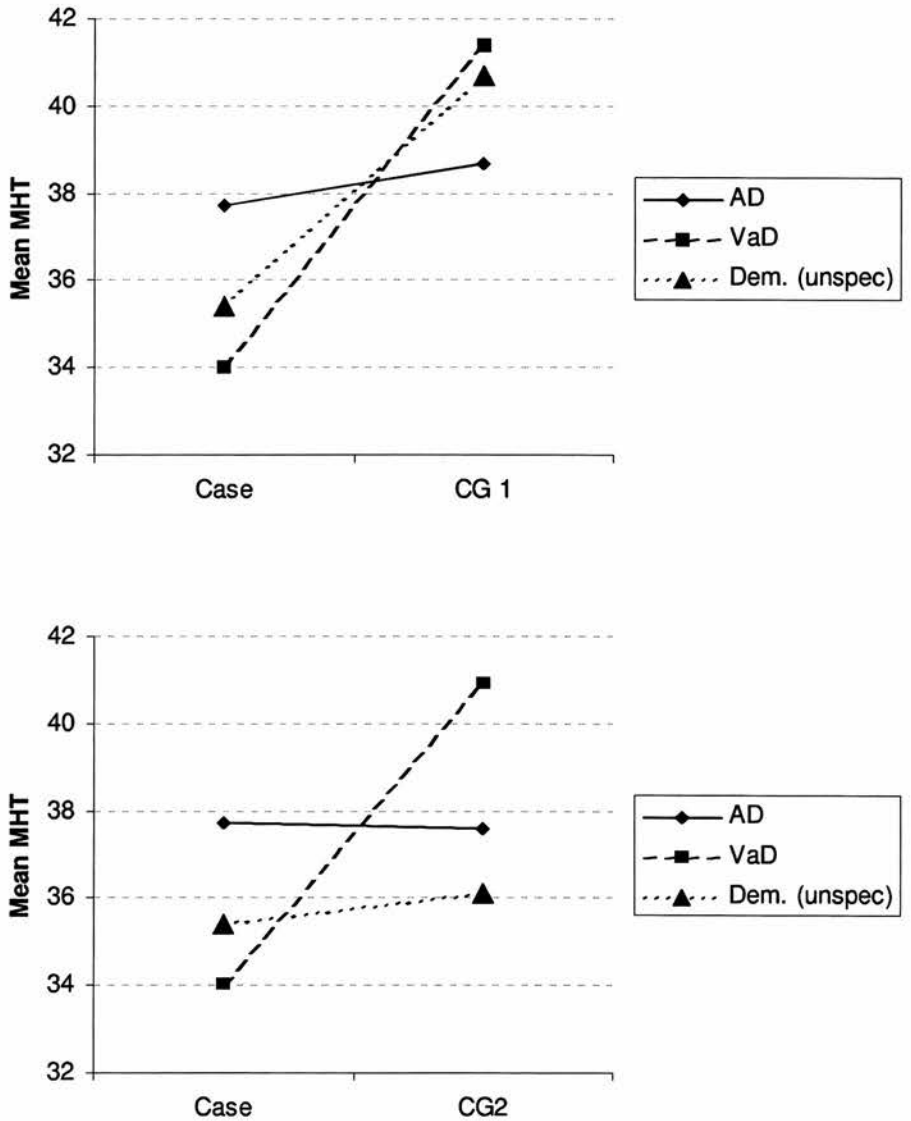
Univariate ANOVA: general linear modeling

The aim of this analysis was to examine whether childhood IQ scores are different between dementia cases and controls, and further to ask whether there are differences in childhood IQ score among different types of dementia.

In this model, MHT score age 11 was entered as the dependent variable. The fixed effects (between subjects factors) in the model were caseness (with two levels, case or control) and type of dementia (AD, VaD and unspecified dementia). Separate analyses are presented with control groups 1 and 2. F ratios and p values are reported for the main effect of caseness. This tests the hypothesis that, overall, people with dementia have lower childhood IQ scores than controls. The main effect of type of dementia is not reported, because the 'groups' in such a comparison would be hybrids of cases and controls. However, the F ratios and p values for the interaction between the two main effects are reported. These address the issue of whether some but not all types of dementia show different childhood IQ scores compared with controls.

The descriptive results are shown in table 2.9 and figure 2.3. AD cases and their controls have similar MHT scores. This is found in comparisons with both control groups. By contrast, the same tables and figures appear to show lower mean childhood IQ scores in people diagnosed with vascular dementia. Again this is found in comparisons with both control groups. The status with unspecified dementia in comparison with their control groups is more equivocal.

Figure 2.3: profile plots of MHT scores in cases and controls



CG = control group

Table 2.9: mean MHT score in cases and controls in people born in Lothian

Type of dementia		n	mean MHT (SD)	t	Sig.
AD	case	63	37.7 (14.0)		
	control group 1	126	38.7 (15.0)	-0.5	p=0.64
	control group 2	122	37.6 (14.9)	0.1	p=0.95
VaD	case	31	34.0 (13.5)		
	control group 1	62	41.4 (14.5)	-2.4	p=0.02
	control group 2	62	40.9 (11.8)	-2.5	p=0.01
Unspecified dementia	case	36	35.4 (16.0)		
	control group 1	72	40.7 (13.9)	-1.8	p=0.08
	control group 2	70	36.1 (14.6)	-0.2	p=0.84

In this model comparing cases to control group 1, cases had lower MHT scores (df = 1, 384, F = 7.84, p=0.005). The interaction between caseness and type of dementia was non-significant (df = 2, 384, F = 1.51, p=0.22). Comparing cases to control group 2, there was no significant difference in MHT score (df =1,378, F=2.34, p=0.13). The interaction between caseness and type of dementia was non-significant (df = 2,378, F = 1.78, p=0.17).

There appear to be lower IQ scores in people with dementia, but even though the interaction terms are non-significant there is a clear indication that people with VaD have lower childhood IQ scores (table 2.9, figure 2.3). It is possible that such an effect could be 'diluted' by the inclusion of the other two dementia groups where there is no such effect or it is equivocal. Therefore, individual comparisons between types of dementia and control groups were performed using t-tests. These analyses show that only the VaD group has a significantly lower mean childhood IQ than its respective control group (table 2.9).

Conditional logistic regression analyses

The aim of this analysis was to test whether low childhood mental ability is associated with diagnosis of dementia in later life. Because this is a matched case-control study, logistic regression analyses was used to look at the association between MHT score and risk of being a case with dementia in later life. Conditional logistic regression calculates an odds ratio and allows for multi-variate analyses. Odds ratios throughout this section are presented as the risk associated with a 10-point increase in MHT score. The standard deviation of the entire population of the SMS1932 was 15.4, so a 10-point change represents about two-thirds of a standard deviation. Once again, because of the effect of migration on the relation between dementia and MHT age 11, the odds ratios for the risk of being a case are presented only in those born in Lothian.

Prior to presenting further results, it is useful as a reminder to note that the control groups are as follows:

Control group 1: matched on age, sex and district of birth registration
Control group 2: matched on age, sex, district of birth registration and paternal occupation

Table 2.10 shows the unadjusted odds ratios for risk of being a case with AD, VaD and unspecified dementia.

Table 2.10: Relationship between MHT score and Dementia sub-types in people born in Lothian

Type of dementia	Control group	Odds ratio (95% CI)	p-value
AD	1*	0.97 (0.79 – 1.19)	0.76
	2†	1.02 (0.82 – 1.28)	0.86
VaD	1**	0.68 (0.50 – 0.94)	0.021
	2††	0.62 (0.41 – 0.94)	0.023
Unspecified dementia	1***	0.76 (0.56 – 1.04)	0.085
	2†††	1.00 (0.76 – 1.33)	0.99

* 63 cases and 119 controls matched on sex, birth registration district and age at SMS
† 61 cases and 119 controls matched on sex, birth registration district and paternal occupational category
** 31 cases and 60 controls matched on sex, birth registration district and age at SMS
†† 31 cases and 60 controls matched on sex, birth registration district and paternal occupational category
*** 33 cases and 63 controls matched on sex, birth registration district and age at SMS
††† 32 cases and 61 controls matched on sex, birth registration district and paternal occupational category

There is no association between childhood mental ability and AD. For unspecified dementia, there was no significant reduction in odds of being a case with increasing MHT. However, for every 10 point increase in MHT score, there is an approximately 40% reduction in the odds of being diagnosed with VaD when compared to matched controls. This odds ratio is similar in both control groups.

The odd ratios after entering covariates into the conditional logistic regression model are shown in table 2.11 for those with AD, table 2.12 for VaD and table 2.13 for those with unspecified dementia.

Table 2.11: Relationship between MHT score and AD in people born in Lothian

Control group	Odds ratio (95% CI)	p-value	Covariates in model
	0.98 (0.79 – 1.23)	0.89	-
	1.00 (0.80 – 1.24)	0.98	Paternal occupational category
1*	0.99 (0.80 – 1.24)	0.95	Maternal age at birth of subject
	0.99 (0.79 – 1.23)	0.87	Paternal age at birth of subject
	0.99 (0.79 – 1.23)	0.90	Length of time parents had been married at birth of subject
	1.01 (0.81 – 1.27)	0.93	-
	1.00 (0.80 – 1.26)	0.97	Age of subject at SMS
2†	1.03 (0.82 – 1.29)	0.82	Maternal age at birth of subject
	1.01 (0.81 – 1.27)	0.91	Paternal age at birth of subject
	1.03 (0.82 – 1.30)	0.82	Length of time parents had been married at birth of subject

* 57 cases and 100 controls
† 59 cases and 110 controls

As may have been expected from the unadjusted results shown above, there is no association between childhood mental ability and late-onset AD.

Table 2.12: Relationship between MHT score and VaD in people born in Lothian

Control Group	Odds ratio (95% CI)	p-value	Covariates in model
	0.75 (0.53 – 1.05)	0.094	-
	0.72 (0.50 – 1.03)	0.073	Paternal occupational category
1*	0.75 (0.53 – 1.06)	0.098	Maternal age at birth of subject
	0.74 (0.53 – 1.05)	0.091	Paternal age at birth of subject
	0.72 (0.50 – 1.03)	0.074	Length of time parents had been married at birth of subject
	0.64 (0.40 – 1.01)	0.055	-
	0.62 (0.39 – 0.99)	0.044	Age of subject at SMS
2†	0.64 (0.39 – 1.03)	0.086	Maternal age at birth of subject
	0.64 (0.40 – 1.02)	0.062	Paternal age at birth of subject
	0.64 (0.40 – 1.03)	0.065	Length of time parents had been married at birth of subject

* 29 cases and 49 controls
† 28 cases and 52 controls

Table 2.12 shows that after entering covariates into the model, odds ratios remain similar to the unadjusted odds ratio presented in table 2.10. Whilst the odds ratios themselves are similar and indeed are similar in the two control groups, the p-value often drops out of significance. This is probably due to the reduced numbers of cases and controls as they drop out of the analyses with incomplete data.

Table 2.13: Relationship between MHT score and unspecified dementia in people born in Lothian

Control group	Odds ratio (95% CI)	p-value	Covariates in model
	0.80 (0.58 – 1.09)	0.15	-
	0.81 (0.58 – 1.12)	0.20	Paternal occupational category
1*	0.80 (0.59 – 1.10)	0.17	Maternal age at birth of subject
	0.80 (0.58 – 1.09)	0.16	Paternal age at birth of subject
	0.79 (0.58 – 1.09)	0.15	Length of time parents had been married at birth of subject
	1.02 (0.76 – 1.37)	0.90	-
	1.02 (0.76 – 1.37)	0.91	Age of subject at SMS
2†	0.99 (0.73 – 1.35)	0.97	Maternal age at birth of subject
	1.01 (0.75 – 1.36)	0.94	Paternal age at birth of subject
	1.03 (0.76 – 1.38)	0.87	Length of time parents had been married at birth of subject

* 31 cases and 56 controls
† 30 cases and 52 controls

Again, as may have been expected from the unadjusted results shown above, there is no association between childhood mental ability and unspecified dementia.

Childhood mental ability and late-onset dementia: discussion

In this study, looking at all of the cases, there would appear to be no association between mental ability in childhood and late-onset dementia (table 2.1). However, the group of cases was very heterogeneous in terms of diagnostic category of dementia and source of case. The results were therefore looked at separately for the three main diagnostic categories, i.e. AD and VaD and unspecified dementia.

When descriptive statistics were analysed, a major effect of migration was identified. Migration is known to have an important association with intelligence (Whalley et al., 2000). Edinburgh, as Scotland's capital, has always attracted migrants from within Scotland and other parts of the UK. Migrators who developed dementia and were cases were compared to population controls from their birth region who were likely to have the characteristics of a population who had not migrated. In table 2.7 we saw that cases from regions outwith Lothian tended to score higher than the controls. This result is put in to further perspective by comparing these scores to the average MHT score for the entire birth region and is shown below as table 2.15.

Table 2.15: MHT scores in cases and controls by birth region including mean scores for regions

	Cases		Control group 1		Control group 2		Region	
Region	n	MHT (SD)	n	MHT (SD)	n	MHT (SD)	**n**	**MHT (SD)**
Edinburgh city	102	37.2 (14.2)	204	41.0 (13.8)	204	38.2 (14.1)	**6695**	**37.3 (14.8)**
W. Lothian	7	34.0 (10.0)	14	33.6 (14.1)	12	36.7 (14.6)	**1764**	**34.2 (14.7)**
E. Lothian	8	37.9 (11.4)	16	35.3 (15.6)	12	38.6 (10.7)	**807**	**34.2 (15.8)**
Midlothian	13	28.5 (18.9)	26	37.6 (18.3)	26	36.3 (16.4)	**1691**	**34.7 (15.3)**
Glasgow	7	38.0 (10.9)	14	34.1 (13.8)	14	33.9 (12.6)	**19765**	**33.2 (15.6)**
Renfrewshire	2	48.5 (16.3)	4	37.0 (17.3)	4	31.3 (18.2)	**5169**	**33.5 (15.4)**
Lanarkshire	11	39.7 (11.1)	22	34.9 (14.8)	20	35.1 (14.3)	**10255**	**32.5 (15.0)**
Ayrshire	2	49.0 (12.7)	4	17.5 (12.8)	2	20.0 (16.9)	**7393**	**31.5 (16.1)**
Roxburgh	3	47.0 (7.2)	6	40.8 (18.6)	4	38.5 (18.1)	**674**	**36.8 (14.7)**
Moray	1	55.0	2	49.5 (2.1)	2	49.5 (2.1)	**888**	**34.7 (15.0)**
Ross	1	34.0	2	24.0 (2.8)	2	26.5 (0.7)	**998**	**30.2 (15.6)**
Dundee	3	29.3 (0.6)	6	39.2 (13.3)	4	45.5 (9.5)	**2941**	**36.0 (14.7)**
Shetland/Orkney	1	67.0	2	26.5 (21.9)	0		**626**	**34.0 (16.1)**
Perth & Kinross	1	52.0	2	40.0 (28.1)	0		**2060**	**37.4 (15.0)**
Inverness	1	59.0	2	26.5 (10.6)	2	33.5 (7.8)	**738**	**32.8 (16.2)**
Dumfries	2	59.0 (0.0)	4	38.0 (8.8)	4	49.5 (11.6)	**1462**	**37.7 (15.2)**
Selkirk	1	37.0	2	28.5 (5.0)	2	18.5 (19.1)	**385**	**37.2 (15.0)**
Argyll	1	70.0	2	40.5 (19.1)	2	44.5 (13.4)	**1013**	**37.0 (15.9)**

The data presented in table 2.15 are vital to consider before interpreting the other data in this thesis. In all but two instances, for cases in this study who had been born in a region outwith Lothian, the cases had higher mean MHT scores than the regional

average. This clearly demonstrates that this association of migration and MHT is a major bias. For this reason, subsequent univariate ANOVA and conditional logistic regression analyses were conducted only for those cases born in Lothian where it can be assumed we are dealing with a more static, less migratory population. Given the degree of difference in MHT between the cases born in Lothian compared to those born elsewhere in Scotland (table 2.8), calculating an odds ratio may have at best hidden a real effect of lower mental ability in cases and at worst artefactually implied that having a higher MHT was associated with an excess risk of dementia.

It was hypothesized that lower MHT scores at age 11 would be associated with a higher risk of dementia in later life. Tables 2.9 and 2.10 show that there is indeed an association between childhood mental ability and late-onset dementia but that this result is restricted to the vascular sub-type of dementia. For those born in Lothian, cases with VaD had a lower MHT than controls (table 2. 9, fig. 2.3). Conditional logistic regression showed that there is approximately a 40% reduction in risk of VaD with every 10-point increase in MHT score age 11. When covariates were entered into the logistic regression model, the odds ratios remained similar (0.62 – 0.75; see tables 2.15 and 2.16) but often dropped out of statistical significance, possibly due to reduced numbers with cases being lost due to incomplete data.

The mechanism of how childhood mental ability is associated with increased risk of vascular dementia may be explored by examining the relation between childhood mental ability and major vascular risk factors. Starr et al. (2004) published data from a collaboration between the SMS1932 and the Midspan study. The Midspan study is a large cardio-respiratory epidemiology study carried out in Scotland in the 1970's. Starr et al. (2004) looked a people who had participated in both studies – in other words they had an MHT score as a measure of childhood mental ability and data relating to vascular risks in mid-life. Lower childhood mental ability is associated with elevated blood pressure in middle age. The authors demonstrated significant negative correlations between MHT score age 11 and blood pressure measured in middle age ($r = -0.16$, $p = 0.001$ for systolic BP, $r = -0.12$, $p = 0.001$ for diastolic BP).

Multiple regression analyses were used to show that the association between IQ at age 11 and BP at midlife remained significant after controlling for father's social class, height, BMI, cholesterol and smoking. The relationship of childhood mental ability and smoking was addressed in another Midspan-SMS1932 study (Taylor et al., 2003). Here, the authors showed that MHT score age 11 did not relate to whether people smoked but people with a higher mental ability (measured before people began smoking in 99.3% of cases) were more likely to successfully stop smoking. Hart et al. (2004) studied cardiovascular outcomes in another Midspan-SMS1932 collaboration. For every standard deviation lower IQ score, there was an 11% increase in relative rate of cardiovascular deaths (coronary heart disease and stroke) in a 25 year follow up period between the beginning of the Midspan studies and 1995. This effect became attenuated after the subjects were older than age 65, which the authors partially attributed to attrition of those with most sever vascular disease.

Thus it may have been predicted that low childhood mental ability is associated with late-onset dementia by its association with vascular risk factors i.e. hypertension, ischaemic heart disease, cerebrovascular disease and smoking. The important thing to note then might be the lack of association with Alzheimer's dementia given the multitude of vascular risks for this disease as discussed above in chapter I.

This result – that higher mental ability gives a lower risk of VaD – is in keeping with other published literature. An excess risk of non-Alzheimer dementia in those with fewer years of education was demonstrated in data from the Framingham study (Cobb et al., 1995). Similarly, Fratiglioni et al. (1991) found an association between lower educational attainment and unspecified dementia but not AD. Likely explanations for this result have included the fact that people with fewer years of education are more likely to smoke and to suffer from hypertension (Garrison et al., 1993). Lower socio-economic status goes along with fewer years of education and is linked to vascular risk factors (Pinsky et al., 1987). In this study, the odds ratio for VaD was not altered after controlling for paternal occupation, which implies that

there may be mechanisms other than socio-economic status that operate to produce this association.

This thesis has failed to demonstrate a link between late-onset AD and mental ability in childhood. This result is very much against published literature suggesting that higher mental ability in childhood or early adult life is associated with lower risk of AD in late adult life (Whalley et al., 2000; Snowdon et al., 1996; Riley et al., 2005). In particular, it goes against previous data from the Aberdeen Birth Cohort 1921 where cases with dementia had a lower MHT age 11 when compared to controls (Whalley et al., 2000).

There is no ready explanation for this discrepancy in result from the data in this thesis and that presented by Whalley et al. (2000). The Aberdeen cases had either AD or VaD. An important consideration is that – as with previous reports of lower mental ability and risk of AD – the Aberdeen cases may have been overdiagnosed with AD and therefore had an ender-estimation of vascular or mixed dementias. However, the Nun Study examined brains at post-mortem and was able to categorise cerebrovascular and AD pathology. Therefore, this is not likely to fully explain results.

There may also be a statistical artefact as a result of a bias in case selection. We know that the cases identified in the LMTC were of above average ability to begin with. For example, the cases with AD identified from patients attending the Lothian Memory Treatment Centre had a higher mean MHT that the mean score fro the entire population of Scotland (MHT = 40.0 for the former, MHT = 34.0 for the latter). However, selection bias cannot fully explain this result: the MHT scores for cases with AD were similar in those cases identified from all three sources (LMTC, REH and RVH; table 2.6).

A third theory could account for the lack of relationship between lower childhood mental ability and AD. There is an association between IQ age 11 and longevity

(Whalley & Deary, 2001). Since advancing age is the single biggest risk factor for the development of AD, it could be that those who have higher mental ability in childhood are more likely to survive to an age where the development of dementia becomes more likely. This could mask an effect of lower mental ability acting as a risk for late-onset AD.

The Nun Study (Snowdon et al., 1996) suggests that there is a relationship between vascular neurological damage and Alzheimer's dementia manifestation. The data presented in this thesis could be taken as general support for a greater vascular contribution to dementia – this will be explored again in chapter IV, where vascular risks and cognitive function in late-life are studied in a group of relatively healthy volunteers.

Childhood mental ability may have a different effect on risk of cognitive decline and frank dementia at different points in the life-course. Richards et al. (2004) looked at the relation between cognitive ability in childhood and cognitive decline in mid-life in a longitudinal birth cohort study for people born in 1946 who had been part of the British birth cohort. Using the AH-4 as a test of mental ability in childhood (age 15), the cohort underwent repeat cognitive assessment at age 43 and 53. There was a significant decline in memory associated with lower ability in childhood. This result was present in men and women and was independent of educational attainment and social class as well as health measures such as smoking, blood pressure and alcohol consumption. The conclusion drawn was that lower ability in childhood was associated with increased cognitive decline in mid-life. However, other researchers have failed to demonstrate a similar relationship between decline in cognition in mid-life and an estimated AH-4 as a measure of childhood mental ability (Rabbitt et al., 2003). It is interesting to note that the age at mid-life testing in this paper was split into age ranges 50-59, 60-69, 70-79 and 80-92. This could imply that the point in the life-course at which the cognitive decline is measured – especially if there are only two measurement points – may influence the degree of decline measured with a

resulting influence on the conclusions which may be drawn about associations between cognitive abilities in early and in later life.

Some literature discussing the role of education, taken by some to be a proxy measure of level of mental ability, was discussed in chapter 1 above. Conclusions were difficult to draw from the diverse range of published data. Discussing some further literature looking at the relation between years of education and risk of dementia in later life may help interpret the data in this thesis.

Cognitive reserve theories should predict that more years of education would lead to the following: protection against cognitive decline and the development of dementia, a slower rate of cognitive decline in those with established dementia, an older age at onset of dementia and older age at death from dementia.

Scarmeas et al. (2006) recently published a paper looking at years of education and rates of cognitive decline in incident AD. They took three cohorts of individuals in New York, examined them for incident AD and used a composite score of initial and repeat cognitive test results to look for decline. Complex generalised estimated equations (GEE) were used to model differential rates of cognitive change. Demographic and health factors were examined in statistical models. There were no associations between age and years of education or age and baseline cognitive test score. The authors found a "borderline" faster decline in composite z-score for those with higher education (β= -0.002, p=0.06), with significant declines in memory and executive speed. Entering vascular risk factors into the GEE model did not change the result. Those with more education had higher composite scores at first visit, and the increased decline persisted after controlling for initial cognitive performance. Interestingly, this paper showed no difference in rate of decline prior to incident AD being diagnosed compared to rate of decline after this point. The conclusions drawn from this paper were that those with higher educational attainment had faster rates of cognitive decline than those with lower educational attainment. This was not thought to relate to age of onset of AD as this was included as a covariate in analyses. Nor

was it thought to be related to a better performance at initial cognitive testing as this was also modelled in analyses. These data are important to consider – if people of higher mental ability (or more years of education) and dementia decline more quickly, then this might bias any association between mental ability and dementia. In other words, those with higher ability are more likely to be diagnosed with dementia than those without as the declining cognitive trajectory is more marked and therefore more likely to come to medical attention.

The findings of Scarmeas et al. (2006) replicate previous studies (Stern et al., 1999; Rasmusson et al., 1996; Teri et al., 1995; Mortimer et al., 1991). Other studies have shown little or no effect of education on rate of cognitive decline (Wilson et al., 2000; Katzman et al., 1998a). Scarmeas et al. (2006) try to relate their findings of excess cognitive decline in those initially more able to the cognitive reserve hypothesis. The argument here is that those with more cognitive reserve require a larger burden of pathology in order to manifest the same level of dementia as someone with lower reserve. Thus, a larger pathological burden leads to more severe brain disease which in turn leads to faster rate of decline. However, once again, the data to support this theory are lacking. The Nun Study showed a greater burden of AD type lesions in those with lower linguistic ability (Snowdon et al., 1996). In addition, a neuropathological study of catholic clergy showed less cognitive decline in those with higher education when years of education was controlled for in analyses (Bennet et al., 2003).

The rate of decline in cognition demonstrated by Scarmeas et al. (2006) did not differ before and after the point of diagnosis of incident AD. This could possibly argue against the idea of cognitive reserve as it might be predicted that higher reserve would lead to more efficient cognitive processing that would protect against decline. It may be that there are complex effects of mental ability (or cognitive reserve), years of education and cognitive decline. For example, it may be that there is an effect of baseline mental ability which is modified by other factors such as years of education.

This study takes this theory further: there may be an additional effect of vascular factors that are related to both childhood mental ability and cognitive decline.

Scarmeas et al. (2006) summarised their results and possible mechanisms underlying these and graphically represented this. This is adapted and shown below as figure 2.4.

Figure 2.4: Cognitive ability and cognitive decline

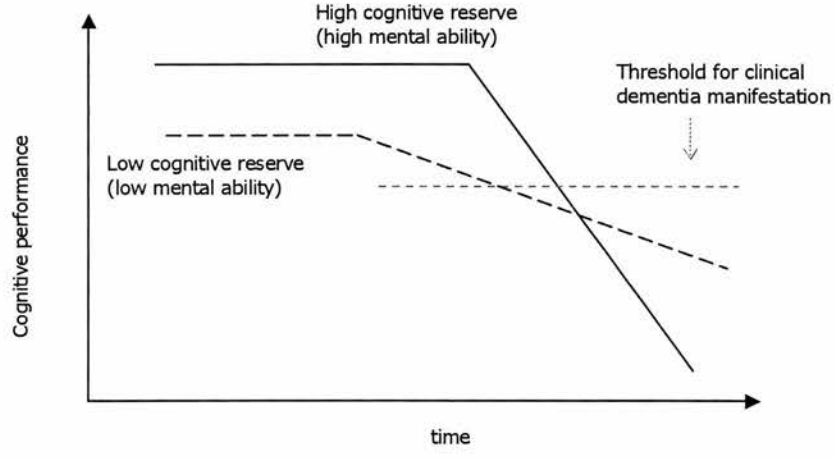


Figure 2.4 graphically demonstrates that there may be a complicated effect of mental ability on subsequent cognitive decline. Other factors may modify the disease manifestation and the slope or rate of decline. Such factors may be for example years of education or other cognitive processes. What this model does not show is that the rate of decline need not be linear. It also does not capture the idea that other disease processes – possibly in particular vascular disease – may alter the point where cognitive decline is diagnosed, the rate of cognitive decline and the threshold at which disease manifests. A further step on from this is that the super-imposed non-

dementia disease may also be a temporary phenomenon, that it alters rate of decline again in a non-linear fashion.

Limitations of this thesis

As a case control study, there are some very important considerations to take into account. The first is case definition and ascertainment. Before trying to generalize the results, it should be determined whether all of the likely cases of people born in 1921 in Edinburgh were found. The census data from 2001 showed that there were 9689 people aged 80-84 living in Edinburgh (General Register Office for Scotland). Assuming that 25% of these were born in 1921, and that 10-15% of these will have dementia, a rough estimate would be that there would be 242-363 individuals. In total, 297 cases were identified. This means that case ascertainment is likely to have been fairly – but not totally – complete. The people with dementia who were not identified may have had different mean MHT scores, potentially leading to a bias caused by case selection. However, the effect of this is likely to be minimal. In addition, those who were not discovered are likely if anything to have had lower MHT scores.

In this thesis data were presented about diagnostic category. In all cases this was based on clinical grounds and ICD criteria were applied. The cases came from three areas – the LMTC, the RVH and REH case registers. Those from the LMTC had a comprehensive diagnostic work-up including brain imageing and in-depth neuropsychological testing from a single neuropsychologist. The patients attending the LMTC were probably not typical of all patients with dementia. They had a limited range of diagnoses – it was a memory clinic designed to manage AD, the patients tended to have mild disease and they tended to come from similar social backgrounds, which were often more privileged. The patients from the REH case register were more typical of patients with dementia in that they span the spectrum of disease severity and diagnosis, they include in-patients, out-patients and they come from all social backgrounds. A disadvantage of using this group is that there is less

diagnostic certainty. However, the coding used was the national disease coding used by the NHS in Scotland and must be considered accurate. The weakness of making a diagnosis of sub-type of dementia is the same in this study as in many other studies of dementia: whilst the diagnosis of *dementia* can be considered sound, the sub-type of dementia is always a presumed diagnosis in life.

Relying on coding by other investigators led to a large heterogeneous group of cases with 'unspecified dementia'. There were no important association between MHT and risk of diagnosis in this group. This is maybe not surprising: this group is likely to have contained various groups including alcohol associated dementia, mixed patterns of dementia, Lewy-body dementia and mis-diagnosed dementias.

A further weakness to consider may be the controls. For this study, population controls were used. This may have led to several weaknesses. The first has already been described: migration. The control groups were likely to represent a more static population and thus have lower MHT scores. For this reason, statistical analyses compared only cases and controls born in Edinburgh and Lothian and excluded migrators. However, we have no data about the migratory status of the controls, who could well have contained important numbers of people who had migrated out of Lothian region. This could explain some of the difference in MHT score seen in those with vascular dementia compared to population controls.

Another feature of the control groups is that they contained people who may have died at a young age, an association with lower MHT scores. We know that the cases survived to at least age 65. This survivor effect may have associated lower scores of controls and higher scores in cases to minimize any possible differences in MHT scores and is an important source of bias to consider when interpreting the results.

As discussed above in chapter 1, this study may have an element of over-matching, which reduces the efficiency of case-control comparison and tends to underestimate the correct odds ratio (Schlesselman, 1982). In other words, the cases and controls

are so well matched on determinants of individual differences in intelligence such as age, birth-region and socio-demographic status that declines in cognition are too small to measure. To combat this, two control groups were used. The data shown in table 2.9 and figure 2.3 raise the possibility that there has been overmatching. Cases with unspecified dementia had a mean MHT score of 35.4 (16.0). Controls matched on age, sex and district of birth registration (group 1) had a mean MHT of 40.7 (13.9) and there was a trend for this to be significant with p=0.08. On the other hand, controls matched on age, sex, district of birth registration and father's occupation had a mean MHT of 36.1 (14.6), a non-significant difference. An advantage of a matched case-control design is that in analysis it controls for the contribution of the matched factor to altered risk of disease. An off-set to this is that it can remove the possibility of fully investigating interactions between other factors and matched variables (Schlesselman, 1982).

Conclusion

Drawing conclusions then, this thesis demonstrates that higher mental ability in childhood is associated with a reduced risk of VaD. It must be stressed that I have failed to demonstrate a link between childhood mental ability and either late-onset AD or unspecified dementia.

The previously demonstrated links between lower childhood mental ability and increased risk of dementia should still be taken as genuine results, despite the apparently contradictory findings in this research study.

Rather, the interesting findings of the link between vascular dementia and lower mental ability in childhood must be explored further. These results interpreted with the vascular association with lower scores on some test of cognitive function (see chapter IV) should be interpreted in the context of the wealth of data (especially epidemiological and autopsy studies) which link vascular factors to AD. This

research could be interpreted as pointing towards vascular factors being important in the development of dementia as it is seen in practice rather than necessarily AD alone.

Chapter III: The estimation of pre-morbid mental ability in dementia

This thesis now discusses the estimation of pre-morbid intelligence, a tool used in demonstrating the decline required to make a diagnosis of dementia. The neuropsychological tool most often used for this purpose (in both research and in clinical practice) is the National Adult Reading Test (NART, Nelson, 1982). This chapter aims firstly to assess the validity of the NART over virtually the whole human life-span by correlating the NART with MHT age 11 and MHT at age 80 (part 2). The hypothesis to be tested here is that the NART should correlate equally well with mental ability in both childhood and in later life. I then report a case-control study in part 3 assessing the validity of using the NART in people with dementia when compared to volunteer controls. This tests the hypothesis that the NART score is not affected by the dementia process and is a 'hold' test.

Part 1. Introduction

To be certain of the diagnosis of a dementing process evidence of a decline over time is required. The nature of assessing this decline, "bring[ing] this subjective clinician's judgement into the scientific arena" (O'Carroll, 1995, p. 83), is crucial. A one-off low score in a test of cognitive function may simply reflect a low prior ability whereas an average or above-average score may yet represent a substantial decline from very high prior ability (Crawford, 1992; Crawford, 2003; Deary, 1995). The estimation of pre-morbid mental ability in an individual with dementia may therefore be important in establishing decline from a previous level of functioning. Because exact records of previous mental ability using a norm-referenced test are rarely found, surrogate estimates of pre-morbid ability have been used. Examples of this have included the use of demographic variables such as years of education or occupational status (Crawford & Allan, 1997). The most commonly used estimate of

pre-morbid intelligence in clinical practice and research remains the National Adult Reading Test (NART; Nelson, 1982).

Crawford (1992) outlined 3 criteria which any estimate of pre-morbid intelligence, including the NART, must fulfil:

1. It must possess adequate reliability.
2. It must correlate highly with measures of psychometric intelligence (criterion validity).
3. It must be largely impervious to the effects of organic brain disease.

Crawford later suggested "that the measure should also be insensitive to individual differences in cognitive decline associated with normal ageing" (Crawford et al., 2001). This is an interesting and important point. As well as describing a feature of the perfect test of pre-morbid ability he raises the possibility that normal, healthy people may show a decline in NART scores associated with normal ageing. In other words, decline in NART score in people with dementia may not be solely due to disease. For pragmatic reasons, then, it would be reasonable to assume that if the NART showed similar decline in health and in dementia, it could be considered to 'hold' in disease and thus remain a valid estimation of premorbid ability.

This part of the thesis will address these important points. The reliability and validity of the NART will be explored, in health and in dementia. This introductory section describes the NART as a neuropsychological test, highlighting why its use has been questioned in dementia. The subsequent section will go on to describe the retrospective validity of the NART across a 69-year interval, whilst the third section will describe a case-control study validating the use of the NART in mild-moderate dementia. A final section discusses the implications of results.

The National Adult Reading Test

The National Adult Reading Test (NART) was introduced in 1978 as the 'new adult reading test' (Nelson & O'Connell, 1978) and later renamed and published as a commercial test, the 'National Adult Reading Test' (Nelson, 1982). The test involves the reading aloud of 50 irregular English words. The words are presented as a written list, and points are deducted if the word is not pronounced completely correct. The test takes only several minutes to administer. Traditionally, the NART is scored as the number of errors, though this is often converted to number of items read correctly in order that the results scale in the same direction as other tests of cognitive function.

All of the words on the NART list are of low frequency and are irregular in that they violate pronunciation rules such as grapheme-phoneme correspondence and syllable stress. Examples of irregular words include thyme (compare with the identically pronounced time), and pint (compared with the regularly pronounced mint). It is thought that this test reflects prior mental ability rather than current mental ability. The rationale behind this is that in order to score correctly, the person taking the test must have come across the word before and have the word stored in a form of long-term memory. If the word is unknown to the testee, and current cognitive resources alone are deployed (in the form of following pronunciation rules), then the subject will tend not score correctly.

The number of NART errors is converted to an IQ type score following instructions given in the test manual. Thus, if estimated prior IQ (NART) differs substantially from measured current IQ (e.g. WAIS), then this is taken as evidence of cognitive decline.

From a psychometric test point of view, the NART fulfils the first and second of Crawford's criteria outlined above. The NART has excellent reliability. The inter-rater reliability of the NART is extremely high, being reported as ranging from 0.96

to 0.98 (Crawford et al., 1989). The test/retest reliability is similarly high at 0.98 (Crawford et al., 1989). It also has good criterion validity: the NART is able to predict 72% of verbal IQ when the full WAIS was used to measure IQ (Crawford et al., 1989). Part 2 in this chapter of the thesis will explore the retrospective validity of the NART across virtually the whole human lifespan.

The NART in dementia

Two facts underlie the basis for the NART in practice; firstly, word-reading ability and general intelligence are highly correlated in healthy adults and, secondly, pronunciation of words is relatively well preserved in dementia (Nelson & McKenna, 1975). Hence, "since vocabulary correlates best with overall ability level and tends to resist the dementing processes better than any other intellectual attainment, the residual vocabulary of patients with dementing conditions may be the best indicator of premorbid mental ability." (Lezak, 1995, p. 551). In the paper giving the original description of the NART, Nelson & O'Connell (1978) compared 40 patients with bilateral cortical atrophy to a control group of 120 individuals. The cortical atrophy group were older (mean age 58.0, SD = 12.0) than the control group (mean age 48.0, SD = 12.0), $t = 2.98$, $p < 0.01$. They also had a significantly lower verbal IQ as measured by WAIS (VIQ=94.8, SD = 14.4 for those with atrophy, VIQ=108.5, SD=12.0 for controls, $p < 0.01$). Despite this, there was no difference in the number of errors on pronunciation of the NART words between the groups (mean 23.9 errors [SD = 11.2] in atrophy group, mean 22.4 errors, [SD = 10.1] in controls, $t = 0.57$, p=NS.). Thus, the NART was considered to be a 'hold' test; that is, it was deemed to be relatively impervious to the effects of neurological and psychiatric disease. However, in this study, cases were defined by results of CT brain scans rather than evidence of dementia or cognitive decline. This is an important distinction – cortical atrophy is a rather vague concept. Not all people with cortical atrophy demonstrate cognitive decline and not all people with dementia have abnormal CT scans.

O'Carroll et al. (1987) identified 3 methods of assessing whether or not the NART is a valid estimate of pre-morbid ability in dementia:

1. Cross-sectionally comparing NART score in cases with dementia to healthy controls (as in the original description of the NART).
2. Correlation of the NART and a measure sensitive to current cognitive status in people with dementia.
3. Exploring decline on NART score on longitudinal testing, contrasted with decline in other dementia sensitive measures with disease progression.

There is a fourth method. The NART could be compared to an alternative method of estimating pre-morbid ability, such as the use of demographic variables. If each method yielded equivalent results, even in the presence of dementia, then the NART could still be considered a valid estimator of pre-morbid ability. It also follows that dementia severity may be an important factor to consider when assessing pre-morbid ability. For example, if people with moderate dementia perform worse than people with mild dementia, this could be indicative that NART score is significantly affected by current cognitive status. Conversely, no evidence of decline in NART score as a person's disease progresses from mild through to severe disease would be confirmatory that the NART is indeed a 'hold' test.

The validity of the NART in dementia: a literature overview

Studies employing all four of these techniques have been used and have led to conflicting results. This has cast doubt as to whether or not a person's NART performance is truly impervious to cognitive decline. Several studies have replicated the original findings that word reading ability is unaffected by the presence of cognitive decline (Nebes et al., 1984; Cummings et al., 1986; O'Carroll & Gilleard,

1986; Crawford et al., 1988; Bright et al., 2002). Nebes et al. (1984) looked at semantic memory problems in Alzheimer's disease. As part of this study they compared 20 cases with 20 controls on NART testing. Those with AD had a mean score of 23.0 (SD = 8.8) whilst the healthy controls had a mean score of 28.9 (SD = 8.0). There was no statistical difference between these two groups, despite the fact that those with dementia scored almost a whole standard deviation lower than controls. Cummings et al. (1986) examined 13 subjects with probable AD and looked at a variety of reading tests. Their subjects' MMSE scores ranged from 1 – 19. This group had a mean NART score of 17.2 (no SD stated). They concluded that "inspection of the distribution of scores revealed no relation between test performance and dementia severity." (Cummings et al., 1986, p. 319). This apparent lack of relation must be tempered by the fact that the numbers of subjects are very small and there was no control group. In addition, no correlation between NART and MMSE is reported, and the authors themselves admit that there is more variability on NART score than on other reading tests. O'Carroll & Gilleard (1986) recruited 30 attenders from a psychogeriatric day hospital. The subjects completed the NART, Mill Hill Vocabulary Scale (MHVS; Raven, 1982) and a survey version of the Clifton Assessment Procedures for the Elderly (CAPE; Pattie, 1981). This latter test is sensitive to increasing dementia severity. Although the correlations were not published in the paper, the authors reported no associations between the NART and the CAPE survey, concluding that the "findings of this small study would tend to favour the view that...the NART...[is] relatively unrelated to measures of dementia severity." (O'Carroll & Gilleard, 1986, p. 157). Crawford, Parker & Besson (1988) evaluated the NART as an estimate of pre-morbid IQ in various organic conditions, including Alzheimer's dementia (n = 14) and multi-infarct dementia (n = 8). Subjects were recruited from a regional dementia project, and were matched to controls who were all healthy volunteers (matched on age, sex and education). There was no difference in NART estimated IQ in either of the pathological groups when compared to normal controls, though the authors rightly point out that these results must be sceptically viewed because of the very small numbers.

These findings are balanced by studies which find the opposite, that performance on the NART does in fact decrease in dementia. Stebbins et al. (1990) examined 199 people with dementia (with AD, VaD and mixed disease), comparing them to 26 controls (who were all spouses of cases). Cases were split into "very mild", "mild" and "moderate/severe" groups based on a dementia severity scale, the Mattis Dementia Rating Scale (Mattis, 1976). For the whole group, dementia patients' NART estimated IQ was lower than controls ($F = 20.5$, $p < 0.001$), although post-hoc analysis showed that very mild patients did not differ from controls. ANOVA revealed main effects for dementia severity ($F = 22.3$, $p < 0.001$), for educational level ($F = 29.4$, $p < 0.001$) and an interaction between education and dementia severity ($F = 4.8$, $p < 0.01$). The authors concluded that the NART was valid only for estimating pre-morbid IQ in very mild dementia. Paterson et al (1994) discovered that performance in the NART and in other tests of reading ability was highly sensitive to severity of Alzheimer's disease. In this cross-sectional study, 25 control subjects were compared to 45 patients who had AD diagnosed by NINDS-ADRA criteria and who were classified as having minimal (MMSE 24-30), mild (MMSE 14-23) or moderate (MMSE $\leq$13) disease. Even those with minimal dementia had a lower mean NART score than the control group. ANOVA confirmed significant differences between the groups ($F = 18.03$, $p < 0.001$), despite the fact that they were well matched on age, sex and years of education. These results were essentially replicated by O'Carroll et al. (1995). They took 68 patients with a diagnosis of AD (recruited from a group who had volunteered for a PET scan study). The severity of dementia was classed as minimal, mild and moderate according to the operational criteria employed by Paterson et al. as outlined above. This showed that there was a significant between-groups difference on NART-estimated IQ ($F = 4.3$, $p = 0.02$), and that NART-estimated IQ represented a serious underestimate when compared to an IQ score estimated from demographic variables in all but the minimally demented group.

The idea that reading ability becomes compromised even in early stages of dementia, and that the NART score declines with increasing dementia severity has been

examined in other studies examining the decline in NART score longitudinally. O'Carroll et al. (1987) recruited 30 people from a psychogeriatric day hospital with either mild or moderate dementia (diagnosed by DSM-III criteria). They collected base-line NART scores then repeated the test after an interval of one year. A non-significant increase in NART errors was discovered, despite a significant worsening of dementia. The magnitude of this change was small: a mean score of 16.6 (SD = 9.7) at base-line, dropping to a mean of 15.1 (SD = 12.3) at 1 year ($t = 1.15$, p = n.s.). The authors concluded that if they had looked at people with more severe dementia, they would have found decline. They did not claim that the follow-up period was short (i.e. only one year), or that numbers were too small to be able to detect a significant change (only 21 individuals completed the second NART test). Fromm et al. (1991) tested 18 subjects with probable AD and 20 healthy controls on a shortened version of the NART – the test comprised of 30 of the original NART words. They repeated this shortened NART annually for a total of 3 visits. The group with AD showed a declining MMSE, as expected, whilst the controls did not. Those with AD scored lower when compared to controls at each visit. A repeated measures ANOVA showed a significant main effect for group ($F = 14.36$, $df = 1,36$) and a significant group by time interaction ($F = 9.89$, $df = 2,72$). These results must also be viewed from a sceptical standpoint; all tests of statistical significance were one-tailed as the authors a priori assumed that those with dementia would perform less well. Cockburn et al (2000) performed a longitudinal study on 78 people with autopsy diagnosed AD ($n = 50$) or clinically diagnosed dementia ($n = 28$). The mean age at entry into the study was 78.6 (SD = 6.7). The mean MMSE was 14.3 (SD = 6.8) and the mean NART correct score was 21.7 (SD = 12.8). Subjects underwent annual testing on the NART until the subject died. Changes over time on the NART score were investigated with multiple regression analyses. This showed that MMSE at entry to the study was a better predictor of subsequent decline in NART scores than the NART at entry into the study. None of age, years of education or duration of dementia were associated with decline in NART score. However, they were forced to conclude that individual differences in cognition were an important feature as there

was no across the board effect, with some people's NART score remaining unchanged despite a falling MMSE, as would be expected in dementia.

Other studies have compared NART estimated IQ to IQ derived from demographic variables. Taylor (1999) assessed 84 people with dementia (43 people with probable AD and 41 people with VaD). He showed that for the whole group the mean IQ estimated from demographic variables (age, gender, educational level and social class) was 100.0 (SD = 7.4), whereas the mean NART estimated IQ was 93.3 (SD = 13.2). He further found that the discrepancy (demographic IQ minus the NART IQ) correlated strongly with NART IQ ($r = 0.83$, $p < 0.001$) but there was no correlation with demographic IQ ($r = -0.01$, $p = NS$). In addition, he correlated a number of cognitive test scores with IQ from NART and demographic variables. He demonstrated that the cognitive test scores correlated more highly with NART estimated IQ than with demographic estimated IQ. This was interpreted as showing that the underestimation of IQ in dementia using the NART was associated with poorer performance on cognitive testing, that "clearly support the suggestion that NART performance is influenced by severity of dementia." (Taylor, 1999, p. 295). Bright et al. (2002) used a similar technique, but found different results. They took 32 patients with probable AD and matched them to 51 controls, based on age, sex, education and occupational level. No significant difference in mean NART estimated IQ was found between the groups. Similarly, there was no significant difference in demographic estimated IQ between the groups. Estimating IQ by the NART method did lead to a lower IQ (106.0 estimated with NART vs 112.6 estimated by demographics) in patients with AD. However, there was a similar difference in estimates in the controls (108.8 estimated with NART vs 112.3 estimated by demographics). They used a combination of NART plus demographics to estimate IQ, and correlated this with current IQ as measured by WAIS. In the AD patients, this correlation did not differ from the NART IQ-WAIS correlation or from demographic IQ-WAIS correlation. Bright et al concluded that these results were "reassuring" supporting the position that the NART's "continued use as a pragmatic

estimate of pre-morbid ability in a number of conditions is warranted." (Bright et al., 2002, p853).

To draw conclusions on the existing literature as to whether the NART is valid in dementia is a difficult task. The studies have tended to be small and have employed disparate methodologies. It is not easy to compare the different case groups directly. Attempting to synthesise these conflicting results, I have summarised the information in Table 3.1. This is not a systematic review, but rather a more general literature review.

Table 3.1: Examples in the published literature of different methodologies employed to study NART in dementia by year of publication

Authors	Year published	Study Type	Main Outcome	number of cases	Results
Nebes et al.	1984	Cross	NART score	20 cases, 20 controls	+
Cummings et al.	1986	Cross	NART score	13 prob AD	+/-
O'Carroll & Gilleard	1986	Cross	Comparing NART to a measure sensitive to dementia	30, dementia	+
O'Carroll et al.	1987	Long.	Decline in NART score over 1 year	21, dementia	+/-
Crawford et al	1988	Cross	NART estimated IQ	14 AD, 8 VaD	+
Stebbins et al,	1990	Cross	Comparing NART estimated IQ in groups with varying severity of dementia to controls	199 dementia, 26 controls	-
Fromm et al.	1991	Long.	Decline in shortened version of NART over 3 annual visits.	18 prob AD, 20 controls	-
Paterson et al.	1994	Cross	Comparing NART score in groups with varying severity of dementia to controls	45 prob AD	-
O'Carroll et al	1995	Cross	Comparing NART estimated IQ in groups with varying severity of dementia to controls	68 prob AD	-
Taylor	1999	Cross	Comparing NART estimated IQ to IQ derived demographic variables	43 AD, 41 VaD	-
Cockburn et al.	2000	Long.	Decline in NART over multiple annual visits	50 AD, 28 dementia	-
Bright et al.	2002	Cross	Comparing NART estimated IQ to IQ derived demographic variables	32 prob AD	+

The balance of evidence would seem to suggest that NART performance is indeed sensitive to degree of cognitive impairment. This "should give serious concern to users of the NART in Alzheimer's disease" (O'Carroll, 1995, p. 85). If the NART is impaired in the presence of cognitive impairment then it can no longer be considered a valid test of pre-morbid ability. However, there are some issues to be considered before accepting this. Firstly, a careful examination of the publication dates (see table 3.1) raises the possibility of publication bias; the more recent published papers have tended to suggest a decline in NART with dementia, whilst those papers finding a replication of 'hold' results are older. Any effect such a publication bias may have is difficult to quantify. Secondly, all of the above studies have the same simple but crucial flaw: they do not take into account a true estimate of pre-morbid ability. Lower childhood ability is itself a risk factor for dementia (Whalley et al., 2000). It is possible that differences observed in NART scores in those with varying dementia severity reflects a difference in underlying mental ability to begin with. I will come back to this latter point, and test the hypothesis that there is no difference in NART scores in a group of people with dementia when compared to a group without, in part 3 of this chapter of the thesis.

Part 2. Retrospective validity of the NART across a 69 year interval

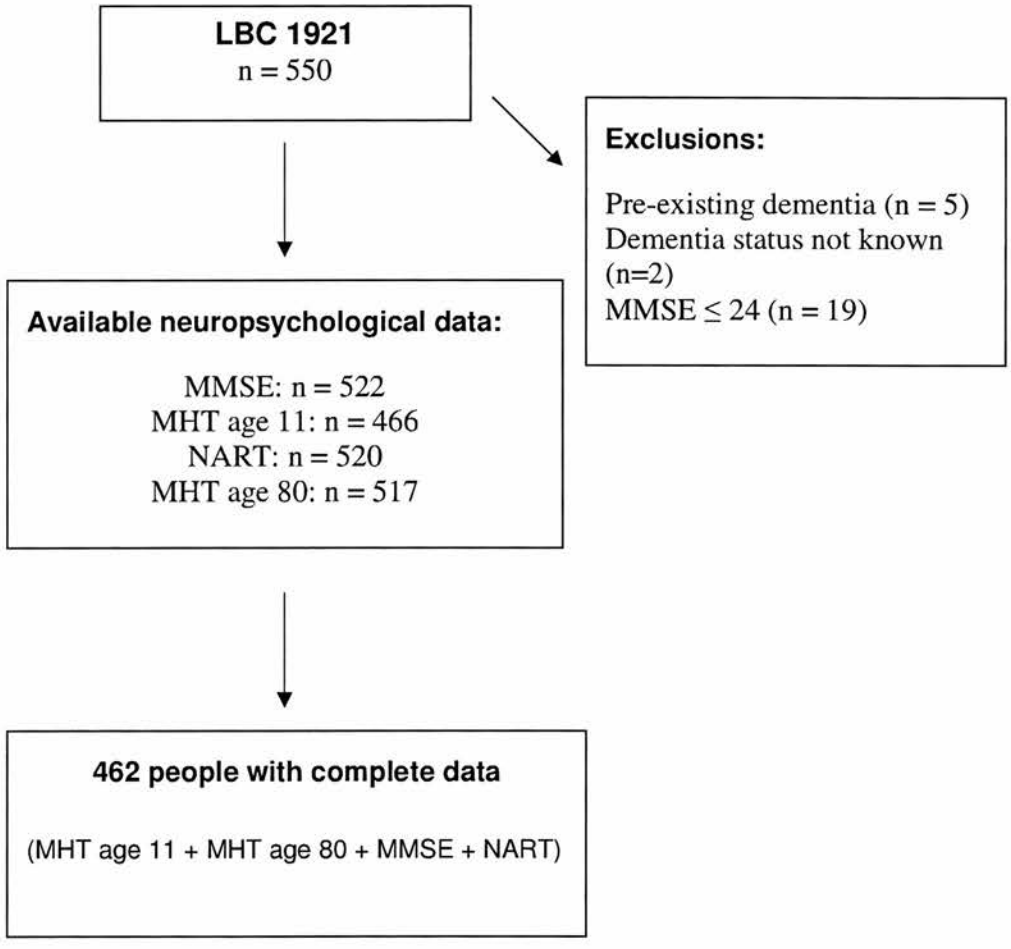
A problem with previous studies of the validity of the NART is that they have relied on concurrent administration of the NART and an IQ type test, rather than comparing NART with a true test of prior ability. The ABC1921 investigators were able to rectify this, and were able to assess the validity of the NART across a 66 year interval by correlating the NART, measured at age 76, with the MHT measured at age 11 and again at age 77 (Crawford et al., 2001). In this section of the thesis I test the hypothesis that, in health, the NART remains an index of prior mental ability and that this validity covers a 69 year interval. This is a replication of results already reported from study of the ABC1921 (Crawford et al., 2001). Corroboration of the validity of the NART in health is an essential prerequisite to establishing its validity in dementia.

Methods

There were 550 participants in the LBC1921 (234 men, 316 women). Those who had a pre-existing diagnosis of dementia were excluded (n = 5, 0.9%). Two were excluded as their dementia status was not recorded. A further 19 people were excluded as they had an MMSE of ≤ 24. MMSE data was not available for 2 subjects, leaving 522 subjects with an MMSE score. An MHT score age 11 was available in 466; a NART score in 520; and an MHT score age 80 in 517 individuals. Variables were first examined and described before Pearson's correlations between NART, MHT age 11, MHT age 80 and MMSE were calculated using pairwise exclusion. Complete data (i.e. MMSE plus NART plus MHT age 11 plus MHT age 80) were available for 462 people. A partial correlation was calculated between NART and MMSE, controlling for MHT age 11.

The numbers of people from the LBC1921 used in this study are summarized below as a flow diagram, figure 3.1.

Figure. 3.1: Numbers of people from LBC1921 used to analyse retrospective validity of the NART across a 69 year interval



Results

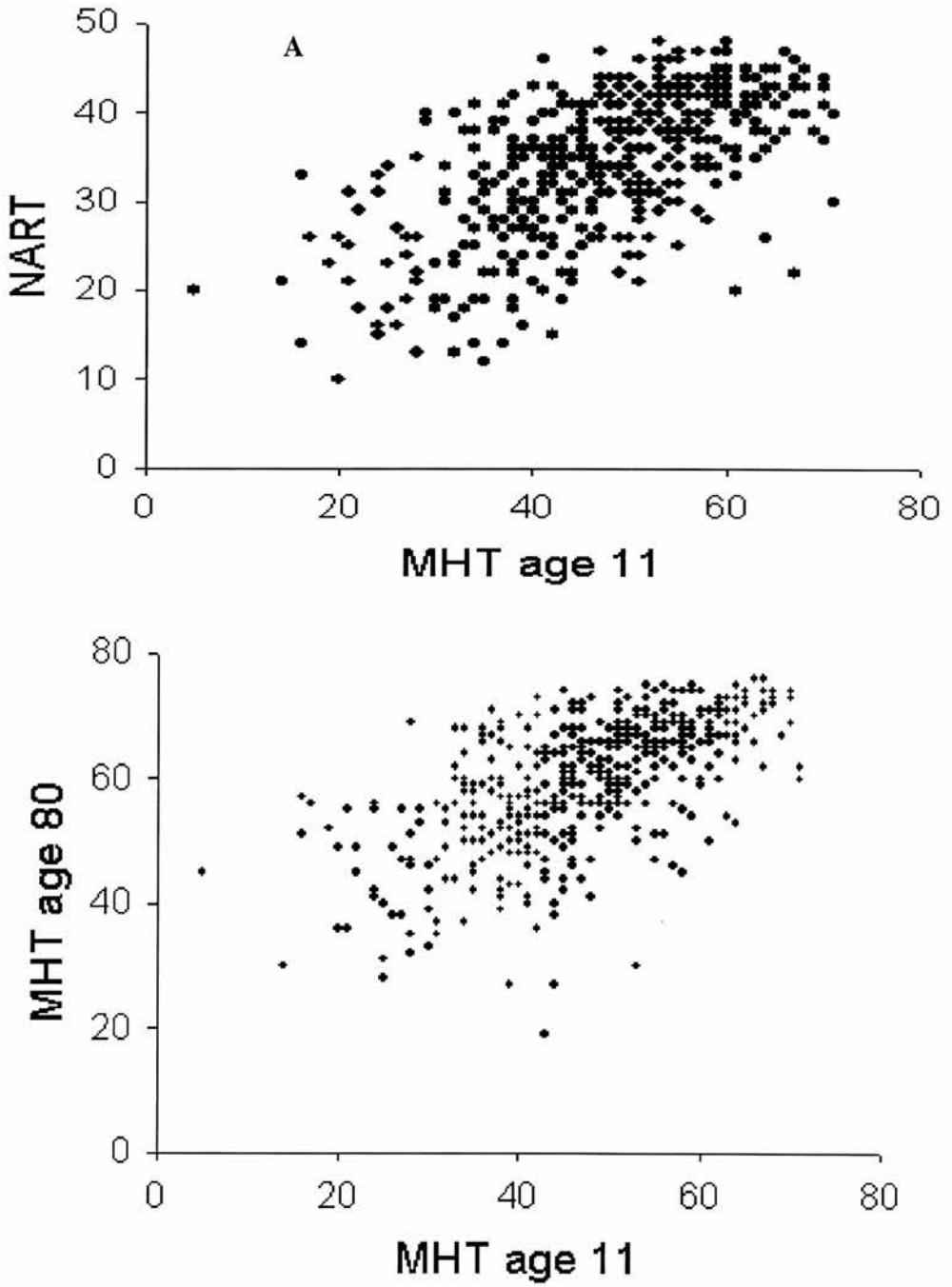
Table 3.2 shows the summary statistics for NART, MHT scores (at age 11 and 80) and MMSE.

Table 3.2: Descriptive statistics for NART score, MHT age 11, MHT age 80 and MMSE

	n	Mean	(SD)	Range
NART Score	520	34.5	(8.0)	10-49
MMSE	522	28.4	(1.3)	25-30
MHT age 11	466	47.0	(11.5)	5-71
MHT age 80	517	59.8	(10.3)	19-76

A scatterplot for of NART vs MHT age 11 is shown in figure 3.2A, whilst a scatterplot for MHT age 11 vs MHT age 80 is shown in figure 3.2B.

Figure 3.2: Scattergram of (A) NART vs MHT-11 and (B) MHT-11 vs MHT-80 for the LBC1921



The comparison of Pearson correlations between NART, childhood and adult MHT and MMSE is shown as a correlation matrix, table 3.3. All correlations were significant, $p < 0.001$.

Table 3.3: Correlations between NART, MHT age 11, MHT age 80 and MMSE

	MHT-11	MHT-80	MMSE
NART	.63	.66	.37
MHT-11		.62	.22
MHT-80			.43

.n = 462. All correlations $p < 0.001$.

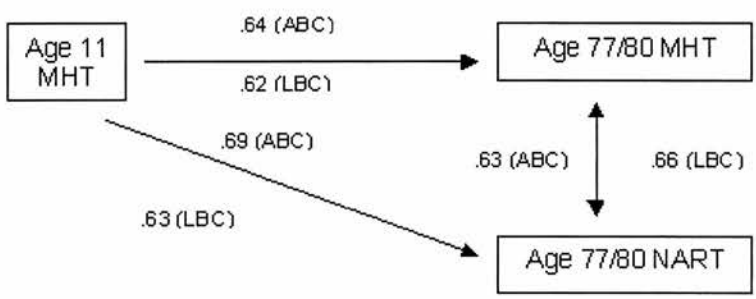
To assess whether the correlation between NART and MHT age 11 differed from that of NART and MHT age 80, a significance test for non-independent correlations (Williams, 1959; Steiger 1980) was used. This showed, in fact, that there was no difference between these correlations ($t = 1.226$, $df = 459$, $p = 0.22$).

In the LBC 1921 the correlation between NART and MMSE was $r = 0.40$, $p < 0.001$. This compares to a more modest correlation of $r = 0.25$ ($p < 0.001$) discovered in the ABC1921. In Aberdeen, however, this correlation dropped to virtually zero and lost significance after partialing out MHT age 11. In the LBC1921, the partial correlation between NART and MMSE, after controlling for MHT age 11, was $r = 0.31$, $df = 461$, $p < 0.001$.

Discussion

The results discussed in this section essentially replicate those previously reported by the ABC1921 (Crawford et al., 2001). This is summarised in figure 3.3, and displays the similarities in the major correlations.

Figure 3.3: Summary of correlations between NART and IQ, comparing ABC1921 & LBC1921



It is a remarkable finding that the NART, administered in late life explains almost 50% of the variance in a test of psychometric intelligence measured in childhood. In this instance, the interval between the tests was 69 years. If the NART was primarily a measure of current ability, then the correlation with NART and a test of current ability (NART-MHT age 80) should be significantly higher than the correlation between the NART and a test of childhood ability (NART-MHT age 11). Given that NART correlates equally with childhood and adult ability, these data can be considered to support the hypothesis that the NART is an index of prior ability.

The different NART-MMSE correlations reported here for the LBC, and for the ABC merit specific attention. However, to be more informative, the results must be compared in people with and without dementia. After presenting such results in the next section, I will return to this later in the general discussion.

The results presented here must be taken in context: the original paper describing the NART (Nelson & O'Connell, 1978) was standardised on 120 people who were all inpatients at the National Hospital for Nervous Diseases, London and who were suffering from extra-cerebral disease. In other words they were not healthy, population controls. The results from the ABC1921 were for 97 people, and the results presented here, from the LBC1921, are from 462 subjects. Hence, this comprehensively confirms the retrospective validity of the NART as an estimate of pre-morbid ability, and that this remains so in healthy people across virtually the whole lifespan. The question of the effect of cognitive impairment on the NART is considered in the following section.

Part 3. Pronunciation of irregular words in dementia: a case-control study

This part of the thesis describes a retrospective case-control study examining the relation between the NART and pre-morbid mental ability in dementia. This overcomes some of the shortfalls of previous studies looking at this relation by using childhood mental ability as a direct measure of pre-morbid mental ability. The aim is to clarify if the NART remains a valid estimate of pre-morbid mental ability in dementia and if not to estimate at which level of dementia the NART begins to fall off.

Methods

In participants of the SMS1932, NART was correlated with mental ability at age 11 in 2 groups: a group who had developed dementia and a control group who had not.

Cases

The Lothian Memory Treatment Centre (LMTC) was set up in 1999 to facilitate the management of dementia in a tertiary referral centre. All patients had a clinical assessment followed by a diagnostic neuropsychological battery assessment including MMSE and NART, which were measured by the same two neuropsychologists. Up to December 2002, 97 patients were identified who were born in 1921 and who had been assessed at the LMTC. The diagnosis of dementia was a clinical one based on ICD-10 criteria. The MHT scores were identified from the SCRE database. NART scores were expressed as number of items correct. There were 29 people with diagnosis of dementia who had had a NART measured and for whom MHT score age 11 was available. We identified a further 16 people with a diagnosis of dementia (either made on entry to the study or at annual follow up) in

the ABC1921. The diagnosis of dementia was based on a clinical interview in 14 cases, on the presence of an extremely low MMSE in one case and in a marked decline in MMSE in one case. ABC1921 participants were administered annual NART and MMSE; the scores on NART and temporally contiguous MMSE from the time closest to the date of diagnosis of dementia were used for this analysis.

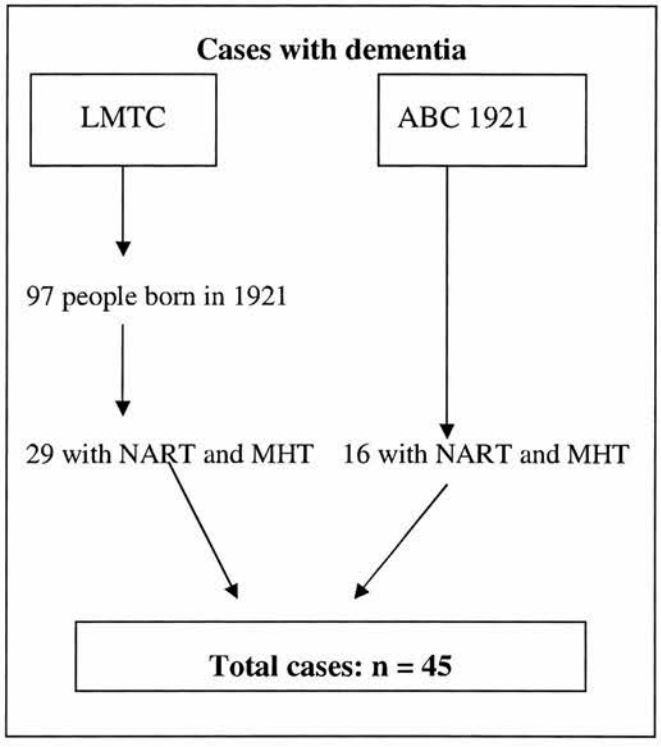
The diagnosis of dementia was probable AD in 57.8% of patients, unspecified dementia in 33.3%, vascular dementia in 6.7% and possible AD in 2.2%.

Controls

The control group came from the LBC1921. Those who already had a pre-existing diagnosis of dementia (n=5) and individuals with an MMSE of ≤24 (n=22) were excluded from analyses. We were able to match 466/522 (89.3%) to their MHT scores age 11. Of these, 464 had a NART performed.

The case selection for this study is summarised below as a flow diagram, figure 3.4; controls came from the LBC 1921 and were summarised above as figure 3.1.

Figure 3.4: case selection to compare NART scores in those with and without dementia



Statistical analysis

Mean differences in MMSE, NART and MHT were tested using the t-test. Linear regression was used to investigate the effect of childhood IQ on NART and MMSE. Pearson's correlation between the NART score, MMSE and MHT age 11 were calculated using SPSS. Missing data were dealt with using a listwise exclusion. We applied a significance test for independent correlations using indepcor, a software programme downloaded from Professor John Crawford's web-site (http://www.abdn.ac.uk/~psy086/dept/psychom.htm; last accessed 02.08.2006).

Results

Table 3.4 shows the differences in age at NART testing, MMSE, NART and MHT age 11 in the dementia and the healthy groups.

Table 3.4: Differences in MMSE, NART and MHT in people with and without dementia

	No dementia		Dementia		
	n	mean (SD)	n	mean (SD)	Sig.
Age at NART	520	79.1 (0.6)	45	79.0 (1.5)	p=0.51
MMSE	522	28.4 (1.3)	45	22.3 (4.3)	p<0.001
MHT	466	47.0 (11.5)	45	38.0 (14.2)	p<0.001
NART	520	34.5 (8.0)	45	28.2 (9.8)	p<0.001

There was no difference in age between the two groups ($t = -0.66$, $p = 0.51$). As expected, however, the dementia and healthy groups differed significantly on MMSE scores ($t = -9.54$, $p < 0.001$). The non-demented group scored at or close to maximum of 30. Most in the dementia group scored in the mild-moderate dementia range: 64% had a score ≤ 24.

The dementia group scored significantly lower on the NART, but crucially also scored lower on the MHT at age 11 (Table 3.4). The mean MHT score of 38.0 in the dementia group is higher than the population mean of 34.5 (SCRE, 1933). The mean MHT of 47.0 in the non-demented group indicates they were relatively able as children. NART scores were adjusted by linear regression for MHT scores at age 11. After adjustment for MHT scores the dementia and non-demented groups no longer differed significantly on NART scores ($t = -1.6$, $p=0.12$). When the MMSE scores were adjusted for MHT scores at age 11, the groups still differed significantly on MMSE ($t = -8.84$, $p<0.001$).

The association between NART, MMSE and childhood mental ability in the dementia and non-demented groups was addressed by calculating Pearson's correlation co-efficients. The correlation matrix for this is shown in table 3.5.

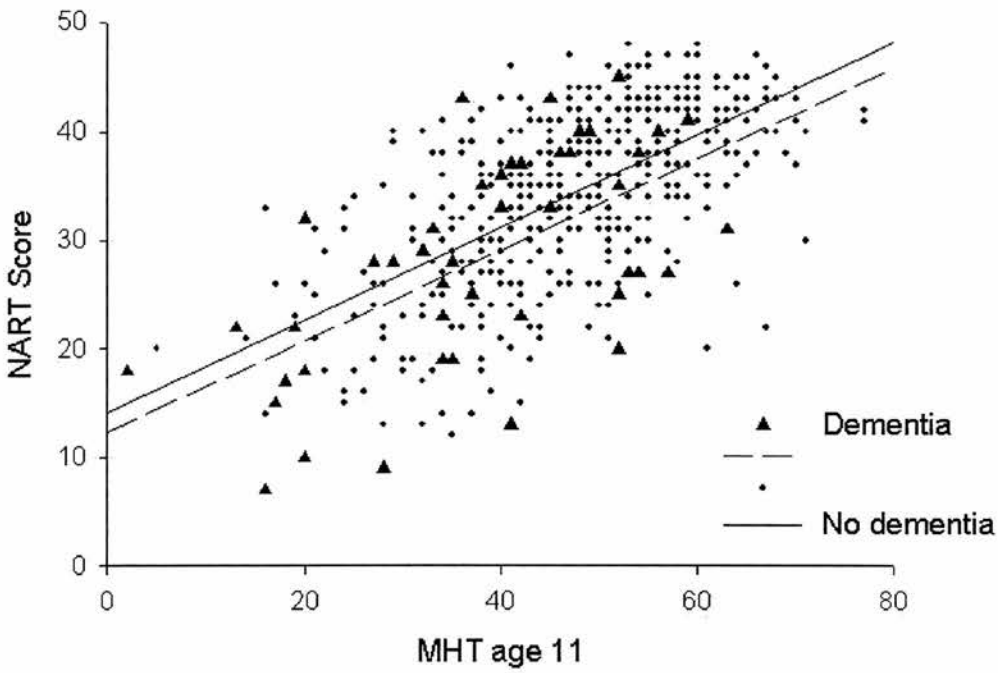
Table 3.5: Correlation matrix for NART, MHT and MMSE in dementia and non-dementia groups

	Dementia (n = 45)		Non-dementia (n = 464)	
	MHT	MMSE	MHT	MMSE
NART	.60*	.51*	.63*	.38*
MHT		.20†		.22*

*p < 0.001 † p = 0.183

Pearson correlations between NART and MHT were similar in the dementia group (r = .60) and the non-dementia group (r = .63). These correlations are not significantly different (z = .239, p = 0.81). The scattergrams and regression lines describing the association between NART and MHT are similar in both the dementia and non-demented groups (Figure 3.5). Regression slopes were compared and did not differ significantly (t = 0.273, df=505, p=0.79).

Figure 3.5: Scattergram with fitted regression lines of NART and MHT in people with and without dementia



It could be argued that the comparable correlations between the NART and MHT are due to undiagnosed or incipient dementia in the non-demented group. To assess this, the highest MMSE scorers in the non-demented group and the lowest scorers in the dementia group were examined. When the non-demented group was restricted to those with MMSE scores of 29 or 30 (usually taken as cognitively normal), the NART-MHT correlation was $r = .63$ ($n=243$, $p<0.001$). When the dementia group was restricted to those with MMSE scores less than 21 (usually taken as important impairment) the NART-MHT correlation was $r = .71$ ($n=14$, $p=0.005$). Again, these correlations showed no significant difference ($z = .445$, $p=0.66$).

The correlation between NART and MMSE merits specific mention. There is a significant correlation in the non-demented group ($r = .38$, $p<0.001$), and also in the

group with dementia ($r = .51$, $p<0.001$). There is no significant difference between these correlations ($z = .867$, $p=0.39$). Partial NART-MMSE correlations, controlling for MHT age 11 were $r = 0.31$ ($df = 461$, $p < 0.001$) for the healthy group and $r = .50$ ($df = 42$, $p < 0.001$) for the dementia group. There is no significant difference between these correlations ($z = 1.37$, $p = 0.17$).

Part 4. Estimation of pre-morbid mental ability in dementia: general discussion

In this chapter of the thesis, part 1 introduced the NART as the most commonly employed test of pre-morbid intelligence in clinical practice and research. Part 2 presented data from the LBC1921 which confirms the validity of this test across a 69 year interval. Part 3 discussed a case-control study of the NART in dementia, the results of which validate the use of the NART in mild-moderate dementia. This goes against the balance of evidence, which could suggest that NART performance is impaired in even minimal cognitive impairment. This final part will go on to discuss the importance of these results.

Interpretation of results

This thesis has described the first study examining the relation between NART and a valid, truly pre-morbid measure of psychometric intelligence in a group of people with dementia compared to a group without. It is remarkable, then, that when we measured the correlation between psychometric intelligence measured age 11 and a test measured approximately 70 years later that we discovered there was no difference between the groups. In fact, the results show a constant relationship between NART and childhood ability in the context of very different levels of current cognitive status (i.e. those in the healthy group who scored at ceiling levels on the MMSE and those in the dementia group who scored lowest on MMSE). This conflicts with the suggestion that NART performance might be sensitive to degree of cognitive impairment.

It may be, however, that the ability to pronounce words holds generally in dementia, declining precipitously beyond a certain cut-off point. Possibly, if we had looked at

more severe dementia, the relationship between NART score and MHT would not have held. If there is a putative cut-off point then this is lower than the range of cognitive impairment in our group: the range of MMSE in the dementia group was 13-30.

The mean NART score in the dementia group was 28.2 (SD=9.8). This is higher than the mean NART score of 21.7 (SD=12.8) in the dementia group in Cockburn's study (2000). This could imply that our dementia group is not typical. The possibility of some bias in selecting the patients cannot be excluded. For example, there may have been a group of individuals where language impairment was a prominent feature of the disease and in whom it would have been impossible to administer the NART. This though is largely unavoidable in a verbal test; the study used data as recorded routinely in neuropsychological assessment, and therefore reflects clinical practice.

Selection bias is unlikely to have significantly altered results. Whilst it is true that cases and controls used in these studies are individuals at the higher end of the cognitive functioning spectrum, after controlling for actual childhood ability, there was no difference in NART score between the dementia and non-dementia groups. It cannot be discounted that this finding is limited to individuals of high mental ability. This, though, seems unlikely by virtue of the very fact that there was a marked difference in mental ability in those with dementia and those without. The finding that NART scores are significantly lower in individuals with dementia and get worse with severity of dementia (Patterson et al., 1994) is to be predicted by the fact that dementia is itself predisposed to by a lower childhood ability (Whalley et al., 2000).

A possible flaw in this study is that we did not clinically examine our healthy group for evidence of dementia. In other words, the fact that we have discovered comparable correlations between the NART and MHT may be due to a degree of undiagnosed or incipient dementia in our LBC1921 group. This seems unlikely. Firstly, in the healthy group, who were all living independently in the community, those with a pre-existing dementia or an MMSE $\leq$24 were excluded. Secondly, the

relationship was no different in those with dementia and an MMSE of < 21 when compared to those in the control group with an MMSE of 29 or 30.

Previous papers have reported a correlation between NART and MMSE and have argued that this confirms that NART performance must be sensitive to current cognitive status. I have presented some of these correlations in table 3.6.

Table 3.6: Some published correlations between NART and MMSE in healthy and dementia populations

Source of data	Dementia/healthy population	Correlation (sig.)
Stebbins et al., 1990	dementia	$r = 0.46$ ($p < 0.01$)
Starr et al., 1992	healthy	$r = 0.49$ ($p < 0.01$)
Patterson et al., 1994	dementia	$r = 0.56$ ("statistically reliable")
O'Carroll et al., 1995	dementia	$r = 0.46$ ($p < 0.01$)
Cockburn et al., 2000	dementia	$r = 0.58$ ($p < 0.001$)
Crawford et al., 2001	healthy	$r = 0.25$ ($p < 0.001$)
This study	dementia	$r = 0.51$ ($p < 0.001$)
This study	healthy	$r = 0.38$ ($p < 0.001$)

Table 3.6 clearly demonstrates that the NART-MMSE correlation is very similar in both healthy and dementia populations. The positive correlation across the board probably reflects a shared inter-correlation between tests of cognitive function; MMSE performance is not independent of underlying mental ability (Crum et al., 1993). If the value of the NART in estimating premorbid intelligence was attenuated in the presence of dementia, then it would be expected that the correlation between NART and MMSE would be different in our two groups. This is not the case, and can be interpreted as further evidence that the NART is primarily an index of prior rather than current intelligence even in dementia. One stumbling block here might be that in the ABC1921 the correlation fell to almost zero and lost statistical significance after partialling out the influence of IQ age 11. This was interpreted as

consistent with the shared variance being a reflection of prior ability, since if it was a reflection of cognitive decline, partialling out childhood IQ should leave the relationship unaffected. These results have not been replicated in this thesis. In the dementia group there was no change in correlation after adjusting for MHT age 11 implying that current cognitive state is contributing more variance to the relation in dementia. In the healthy LBC group the correlation fell slightly but remained significant, implying that the relationship between NART and MMSE is more a reflection of prior ability in health. The NART-MMSE relation may have a similar correlation but for different reasons in health and in dementia.

It has previously been argued that an association between MMSE and NART performance may be perpetuated in severely impaired populations because of degradation in NART performance caused by dementia (Crawford et al., 2001). The results presented here make this unlikely as we have shown there to be no difference in NART score in two very dissimilar groups after controlling for childhood mental ability.

In this thesis, data have been presented on the relation between the NART and childhood ability in dementia. Only NART and MMSE from a single assessment have been presented. I have been unable to examine the longitudinal effects which dementia has on an individual's NART score. Fromm et al. (1991) and Cockburn et al. (2000) showed that NART scores in individuals with dementia decline with time as dementia advances. However, there is no consistent predictable effect of dementia on the NART for a particular person. This is illustrated in figure 3.6, adapted from Cockburn et al. (2000).

Figure 3.6: Cartoon of disparate patterns of decline of MMSE and NART in dementia

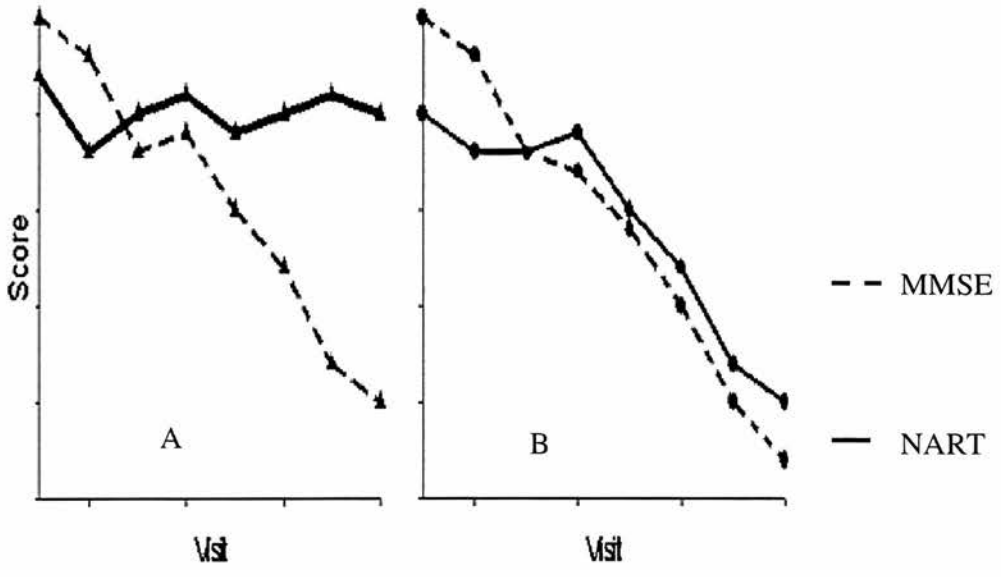
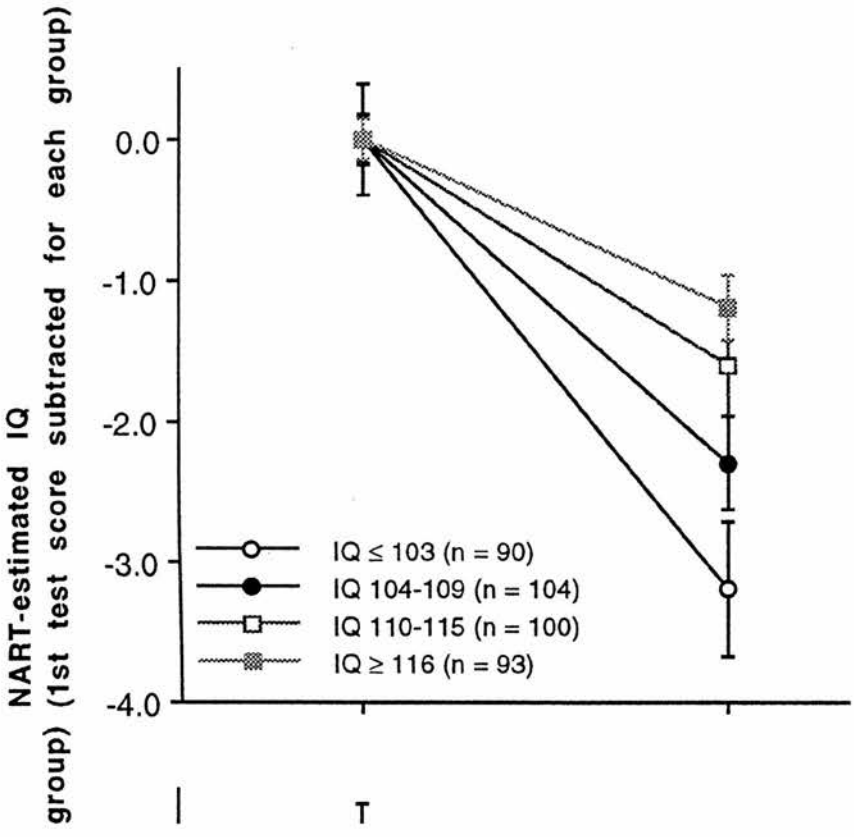


Figure 3.6 part A represents an individual where the NART score holds up despite a progressively falling MMSE (worsening of dementia). Part B illustrates a situation where the NART declines with time as the MMSE declines. Given that childhood mental ability has an effect on NART score when measured at a single point in time, it is not unreasonable to expect that it would also have a profound influence on the rate at which a NART score might decline. A cogent hypothesis would be that NART score would decline less quickly in an individual of higher childhood ability. There is some evidence to back this up, coming from the 'Healthy Old People in Edinburgh' (HOPE) study (Deary, MacLennan & Starr, 1999). This study was able to record a NART, and repeat this measure in a second wave of testing 4 years later, in 387 healthy individuals who had a mean age at entry into the study of 75.1 years (SD = 3.9). Even healthy people showed a decline in NART predicted IQ, albeit minimal. The degree of decline was greater in those who started off with lower predicted IQ. This is demonstrated in figure 3.7, from Deary, MacLennan & Starr (1999).

Figure 3.7: Change in NART estimated IQ with time in a healthy cohort



Thus the decline in NART in people with dementia is not solely due to dementia, as this decline is also evident in healthy individuals. The differential trajectory of decline in people of varying mental ability implies that individual differences in mental ability are an important determinant of future change in NART score. Whether this differential decline is more marked in people with dementia compared to healthy individuals taking into account childhood mental ability has not been tested, and is clearly an avenue for future study.

Some limitations of the data in this thesis

During the interpretation of the data presented in the text above, many weaknesses have been outlined. I will not repeat these but highlight some of the other possible problems with the study of the NART in dementia. The data presented came from the SMS1932, and hence any limitations of this survey hold for our study. These were covered in part 1 of this thesis.

The number of people with dementia studied was quite small – only 45 people. Referring back to Nelson & O'Connell (1978), the NART was originally validated by studying only 40 people with cortical atrophy compared to controls. Also, the studies in the literature have tended to be small as can be seen in table 3.1. This relatively small case group is contrasted with the large numbers of controls (550 individuals). This allows more certainty in drawing conclusions from the data. Perhaps a more fundamental problem with the dementia group was that it was recruited from two separate parts of Scotland, who each thus followed a different diagnostic process, although each centre did employ the same diagnostic criteria. This, coupled with the small number of cases, means that the dementia group must be looked at as a whole. In other words, I have looked at the NART in dementia rather than the NART in AD or the NART in VaD. Conversely, though, this may make the results more generalisable as it reflects current clinical practice; different centres employ different strategies to manage dementia and its subtypes.

It could be argued that we cannot compare the neuropsychological tests as they were performed by a variety of different testers. This I do not feel to be a major weakness: all of the people who administered the NART were fully trained. This thesis has made the assumption that there is an excellent inter-rater reliability, with figures up to 0.98 reported (Crawford et al., 1989). Admittedly, this thesis has not formally tested the inter-rater reliability of the NART.

Validation of the NART – implications for clinical practice

The fact that the use of the NART in dementia has been validated only up to moderately severe disease does not create a major problem for its use generally. Unfortunately, by the time dementia becomes severe, the decline in function required for the diagnosis of dementia is all too evident. It has been argued that estimating pre-morbid intelligence in dementia should use a regression equation based on demographic variables combined with NART errors (Crawford et al., 1990; Willshire et al., 1991). Bright et al. (2002) disputed this, finding that demographic variables were not superior to NART score, and the combination of NART plus demographic variables did not greatly improve the precision of estimating IQ. The results presented in this thesis clearly bolster the position of the NART as an estimate of pre-morbid intelligence in dementia.

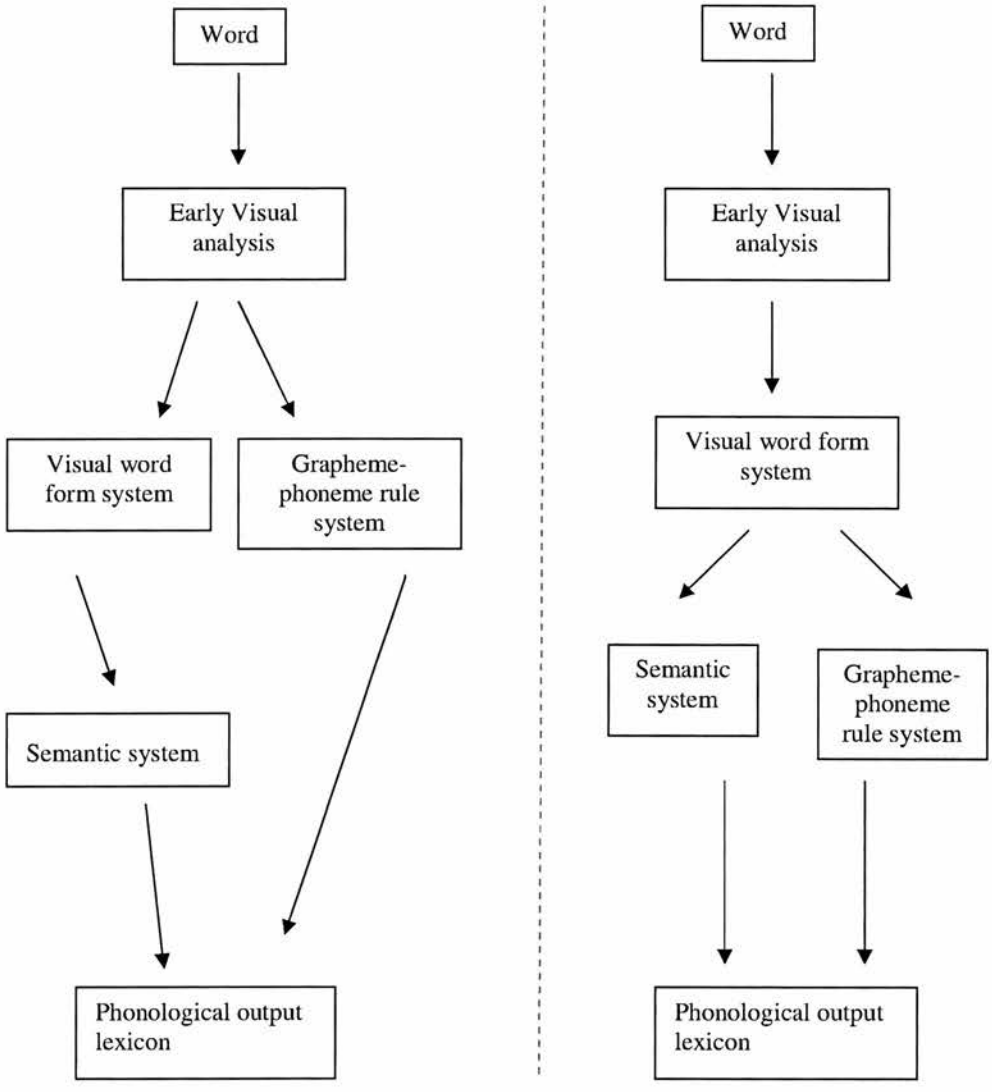
Mechanism of preserved pronunciation in dementia

Why should the reading aloud/pronunciation of irregular words be preserved in dementia? If there is an answer to this question, it is not straightforward. The results presented in this part of the thesis, and the theories of possible underlying mechanisms, pose some fundamental implications for basic science. One way of attempting to answer involves exploration of the theory of mechanisms of pronunciation of irregular words. This seems an appropriate place to begin, since the NART is a test of reading of irregular words. However, we are not necessarily interested in language *per se*, but rather the underlying processes that seem preserved in dementia. Are these words held in a unique 'language' semantic store or is such a semantic store general to many cognitive processes?

One theory of language holds that words are held in an 'orthographic lexicon' (orthograph here is defined as the form of the visual word; it literally means written

straight) and that a single step is required from orthograph to phonological output (pronunciation). However this may not be the case for irregular words. It has been argued that orthographic and phonological information is held in a network of sub-word fragments and that semantic memory processing is vital to give context to the irregular words in the lexicon thus ensuring coherence between orthographical and phonological elements in this network (Plaut et al., 1996). This is in keeping with the dual route theory of reading (Humphreys & Evett, 1985; Coltheart et al., 1993; Besner, 1997). A model of this, adapted from Jobard et al. (2003) is illustrated in figure 3.8.

Fig 3.8: The dual route theory of reading



The dual route theory holds that, after visual presentation of a word and early visual analysis, pronunciation (phonological output) can be achieved via two routes. The first, or direct, route is the lexicosemantic system: for words that do not follow normal pronunciation rules the semantic meaning must be given by the direct association of the word in order for it to be pronounced correctly. The second, or indirect, is grapheme-phoneme route: the auditory representation follows grapheme-

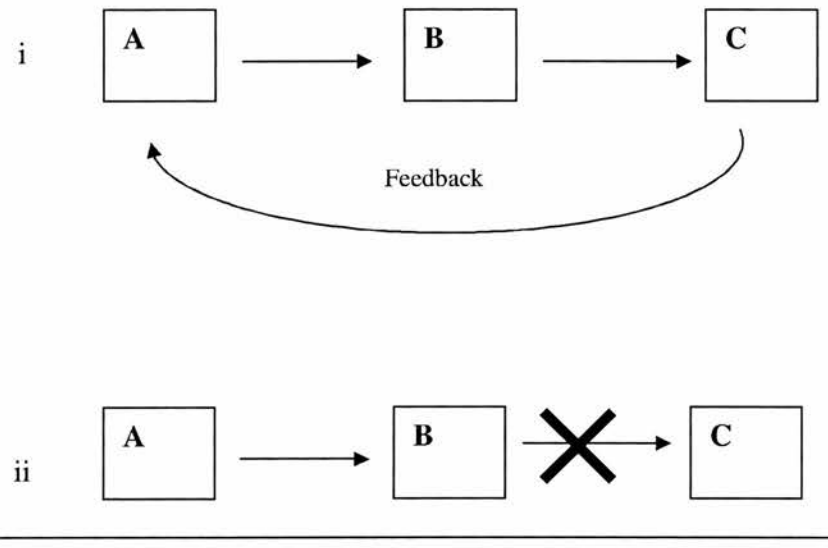
to-phoneme correspondence, which gives meaning to the word and it can then be pronounced. This is thought to be true for regular words. There is some debate as to whether pronouncing regular words involves any further visual word analysis, but for the purposes of this thesis, we will stick to that for irregular words. The dual route theory is not simply theoretical. As early as 1874, Wernicke referred to "wortschatz", translated as "word treasury" and "klangbild", translated as "sound picture" (Wernicke, 1874). Further evidence that semantic processing might be functionally discrete from orthographic systems comes from Farah & Wallace (1992) and Forde et al. (1997) who described cases where patients were able to categorise fruit and vegetables (i.e. semantic knowledge was intact) but were unable to name the actual objects.

There remains no consensus on the precise cognitive processes involved between the presentation of a word in its written form to its accurate pronunciation. Much of the debate surrounds whether the primary process is "phonological" (see for example Lesch & Pollatsek, 1993; Van Orden et al., 1990) or whether orthographic patterns play a larger role (see for example Coltheart et al., 1993; Jared & Seidenberg 1990). Yet more debate is involved in the non-linguistic processes involved in impaired reading aloud. For example, it has been suggested that some reading problems in AD arise from impaired visual information processing (Glosser et al., 2002). Glosser et al. (1999) showed that AD patients were more impaired at reading exception words than at spelling the same words to dictation. Other cognitive 'modules' which are impaired in dementia include attention. Perry et al. (2000) took a group of 27 individuals with AD (minimal and mild disease). They demonstrated that whilst 96.3% were impaired on tests of episodic memory, 63% were impaired on tests of attention (Test of Everyday Attention; Robertson et al., 1996) and only 44.4% were impaired on tests of semantic memory. Equally pertinent is the finding that people with dementia have longer response times (RTs) when presented with a list of words to read, and that this gap widens with time despite a relatively slower decline in semantic memory (Strain et al., 1998). Thus yet another cognitive process i.e. executive functioning is implicated as having an effect on reading ability. Clearly,

the correct pronunciation of a word after its presentation in visual format is a complex process. It seems unlikely, then, that this will involve a single step or a single cognitive function.

Anatomical and functional aspects of language have been studied since at least the mid-19th century. Attempts to localise cognitive function using imaging techniques may well be impossible (Coltheart, 2004). Figure 3.9 illustrates a model of a potential cascaded cognitive system made up of 'cognitive modules'.

Fig 3.9: A representation of a modular based cognitive system



X marks interruption to connection between modules

In this system, if one were trying to image the brain of a person doing a task that involves cognitive module A, then modules B and C would also activate irrespective of their association to module A (fig 3.9i). Hence, any anatomical information gleaned by the scan cannot be considered to be solely due to that of activation of cognitive module A. Similarly, a lack of activation of a brain area does not indicate that a particular module is not involved. If a connection between modules were

interrupted (fig 3.9ii) then module C would not activate yet its underlying process remains intact. A practical example of this might be that semantic knowledge remains intact, but cannot be accessed as retrieval pathways are degraded.

A further difficulty is the interpretation of results in an individual with disease. Compensatory strategies may minimise apparent deficits. This may occur on different levels. For example, an individual with dyslexia may read accurately using a serial letter-by-letter strategy, contrasting with traditional theories of how reading is achieved. This apparent 'normal' reading mimics 'normal' cognitive processes, but no true insight could be gained as to actual cognitive processes.

Another potential example is where an individual with dementia may accomplish the same task as a healthy individual by recruiting a different brain areas or neuronal networks. Areas in anatomically close proximity may be involved in disease, apparently creating an association but the function in these brain areas may not be linked. In other words, once again, function cannot always be tied to anatomy and/or pathology.

This problem lies at the very heart of cognitive neuropsychology. It has led one leader of the field to state: "I don't know of any examples in which there is current consensus as to the cerebral localisation of any module of any cognitive system on the basis of cognitive neuroimaging data." (Coltheart, 2004). It is not clear how this debate may be resolved. Animal studies may well convincingly identify widespread neuronal networks (Hoffman & McNaughton, 2002). The actual significance of this in a coherent animal model let alone a human correlate is less obvious (Fries et al., 2003).

Despite the theoretical problems with neuroimaging, this technique remains a valuable research tool. "In the most general sense, neuroimaging provides a tool for localizing and measuring the activity of brain regions that are recruited during the performance of a cognitive task" (Fiez & Peterson 1998, p. 914). There have been

many studies of functional brain scans attempting to localise brain function during language tasks. These have mainly been Positron Emission Tomography (PET) and functional magnetic resonance imaging (fMRI). Functional neuroimaging studies yield further evidence that the process or (more-likely) processes involved in language production are not simply delineated. Both cerebral hemispheres are involved in language comprehension (Caplan, 1992) whilst recent fMRI work on language activation showed that this is lateralised to the dominant hemisphere in 94% of cases and is symmetric in 6% but that both hemispheres were involved to some degree in all (Springer et al, 1999).

Further studies attempting more detailed localisation than this have been reported. Fiez and Peterson (1998) gave a colloquium paper addressing neuroimaging studies of word reading in which they asked the question "do results converge across studies?" They reviewed nine studies in which subjects read aloud single words. They found that the number of activated brain regions varied from 2 to 32. They cited differing scanning techniques (PET vs fMRI), varying task-related protocols, technological limitations, along with anatomical and cognitive differences in individuals as the reasons underlying this difference in brain areas discovered to be important in word reading.

A discourse on possible and probable language areas in the brain is not essential to this thesis, and I have therefore avoided providing such a list. Rather, I use the lack of consistency across studies to argue that there is currently no coherent platform from where to argue the precise mechanisms underlying the results presented in this part of the thesis. Interestingly, Jobard et al. (2003) were able to perform a meta-analysis of 35 neuroimaging studies evaluating the dual route theory of reading. They were able to conclude that "Despite methodological and experimental differences inherent to the comparison of studies issued in worldwide laboratories, a consensus can be drawn within the technique's spatial limitations as to which sites are critical for identified processes." (Jobard et al., 2003, p. 710).

It remains too far a leap to conclude that preserved pronunciation in dementia is causally related to any cognitive or neural properties of brain regions of interest identified in functional scans performed in healthy individuals. Clearly further work is merited. Functional imaging – specifically for the task of reading the words contained in the NART – comparing individuals with and without dementia should be performed. Any results obtained must be interpreted in the light of individual differences in underlying mental ability.

Accepting that there are many aspects to debate on what are the precise mechanisms involved in language production, we are left with attempting to interpret the results presented in this thesis in light of the most plausible of current theories. The accepted wisdom is that Alzheimer's disease leads to "a loosening of semantic ties and concept formation that produces a loss of the associated links of words, and the things they represent." (Thompson, 1988, p. 132). Patterson et al. (1994) put forward the very plausible theory that the important step in the reading aloud of words was the retrieval of those words from the mental lexicon using semantic memory. In dementia the ability to read words aloud should decline as semantic memory declines with disease progression. They discovered that reading aloud of regular words, exception words (the NART) and non-words was impaired in dementia and concluded that this "established that reading is not a spared ability in [AD]" (Patterson et al., 1994, p. 405). Our results conflict with this conclusion. They indicate that when childhood mental ability is controlled for there is no longer a difference in NART score between a group who have dementia and a group who do not. A possible explanation for this lies in the fact that in dementia not all cognitive domains decline at the same rate with language and memory functions frequently impaired at an early stage. Our results could be taken to suggest that where there is greater childhood mental ability semantic memory processing remains relatively intact. Alternatively, it may be that in those of higher ability, neurological damage is compensated for over for a broader range of cognitive impairment, tying in with theories of cognitive reserve. One final theory is suggested; the results presented here could be taken to mean that semantic memory is less important in the pronunciation

of irregular words than has previously been thought, pointing the way to separate, but as yet unidentified, neural mechanisms.

Rather than an effect of disease on the brain, there may be an effect of the brain on disease. It is possible that there are brain specific processes (be they anatomical or functional) underlying the preservation of this ability in dementia. Strain et al. (1998, p. 155) state: "As a late-acquired skill, both evolutionary and developmentally, reading seems a likely candidate for a cognitive ability – or rather a set of component abilities – that would rely on more fundamental operations that the brain evolved to accomplish." This quote is illustrative of an important point: the fact that the NART is preserved in dementia may be nothing to do with language production per se. It may be that the NART taps into general 'semantic' processes.

This lengthy analysis of language in dementia has been essential because the NART is a verbal test. In the final analysis, though, it may not be true to say that reading aloud of irregular English words is preserved in dementia. It may be more accurate to suggest that the apparent lower scores in people with dementia are a reflection of individual differences in underlying mental ability. Those with dementia have lower ability in childhood and lower ability in adulthood and this stability in individual differences persists even after the onset of dementia.

The estimation of pre-morbid mental ability in dementia: conclusion

This part of the thesis was concerned with the estimation of pre-morbid mental ability in dementia. The single most important neuropsychological test employed in clinical and research settings is the NART. This thesis was able to demonstrate that the NART correlates equally highly with current measured IQ than with IQ measured

in childhood. Remarkably, this has proven to be the case over a 69 year interval. After setting the scene that the NART has an extremely high validity, attention was drawn to the balance of evidence suggesting that NART performance was poorer in dementia, and that performance further degrades with disease progression. Using a case-control study this thesis has shown that people with dementia do indeed have lower NART scores. However, after adjusting for childhood ability there was no longer a difference in NART score between a group of people with dementia and a group without. This establishes two things. It essentially validates the use of the NART as an estimate of pre-morbid ability in mild-moderate dementia in a way that not even the test's authors were able to do. It also establishes that pronunciation of irregular words is preserved in mild-moderate dementia. This conflicts with current theories of why dementia negatively affects language production, pointing the way to novel neural mechanisms. This thesis is therefore important in clearly identifying hypotheses for future testing.

Chapter IV: Childhood mental ability, vascular risk and late-life cognition

In chapter II of this thesis, lower childhood mental ability was shown to be associated with vascular dementia in later life. There was no association found between childhood mental ability and late-onset AD. In chapter I, strong evidence was presented to support the suggestion that AD and cognitive decline may have a vascular cause. This chapter of this thesis aims to explore this further. If the contribution of lower childhood mental ability to later life risk of dementia is mediated through vascular risk then we might expect to find an association between MHT score age 11 and ECG changes in later life.

I describe a case-control study which aims to test the hypothesis that ECG changes (of ischaemia, LVH and conduction defects, taken as a marker of vascular disease) are associated with lower childhood mental ability age 11. Additionally, I test the hypothesis that these ECG changes are associated with poorer tests of cognition in later life, in particular verbal fluency as a test of executive function.

Introduction: electrocardiographic changes and cognitive decline

The ECG is a very common test: virtually every adult admitted to a UK hospital will undergo this investigation. It is primarily used in the diagnosis of and screening for cardiovascular disease (CVD). Changes commonly found include ischaemic changes, conduction defects and ventricular hypertrophy. ECG changes may be considered a marker of vascular disease; this commonly held belief is explored and challenged in detail later in this thesis.

Despite the ECG being a very common test, the link between ECG changes and cognitive function has not been extensively studied. In fact, only two studies have done so. The Rotterdam study was described above. Using the MMSE as a measure of cognitive function, Breteler et al. (1994) showed that people with ECG evidence of previous myocardial infarction had a lower mean MMSE. Those with ECG changes had a mean MMSE of 26.7; those without ECG changes had a mean MMSE of 27.4 (after adjusting for age, gender and education). They also found a shift in the distribution towards lower MMSE scores. Importantly, they took 24 as a cut-off and showed that 11.3% of people with ECG changes of previous MI had an MMSE of <24, whereas 5.6% of people without these ECG changes had an MMSE of <24.

The Caerphilly cohort (Elwood et al., 2002) also looked at ECG changes and cognitive function. This study took a large representative group of men from South Wales (n = 2154) who had been studied to look at associations between cognitive function and vascular disease. These men were examined prospectively in phases. Cognition was assessed when the men were between 55-69 years of age (1870 men agreed to cognitive testing); the tests used were the AH-4 (Heim, 1970) which is a test of general intelligence, the CAMCOG (Huppert et al., 1995) which includes an MMSE and Choice Reaction Time (CRT). An ECG was analysed and a diagnosis of "probable ischaemia" was made on the basis of the presence of "major or moderate" Q-waves. People who had had a stroke were excluded. After controlling for age, social class and mood at the time of testing, the men who had ECG changes of "probable ischaemia" had a lower MMSE, and a lower CAMCOG. Although the mean scores were not presented, this was equivalent to 15% of a standard deviation for the MMSE and 14% of an SD for the CAMCOG. For the MMSE, this was equivalent to a score lower by 0.3 of an MMSE point. The men with ECG changes also had lower AH-4 and CRT scores, although not significantly so.

What does this mean? Both the above studies have shown a reduced MMSE in people with ECG changes of MI or ischaemia. The effect is very small (0.3-0.5 of an MMSE point), and the clinical significance must therefore be debatable. However,

the men studied in the Caerphilly cohort were young and cognitively healthy (age range 55-69), and so we would expect a marked ceiling effect on the MMSE, with very little variability in MMSE scores in this group. The Rotterdam study also showed a similar ceiling effect in MMSE score. Therefore the reduction in MMSE score although small may yet be important. It is impossible then to ignore the fact that ECG changes are associated with a small but possibly important reduction in cognitive function as measured by MMSE.

ECG changes as markers of vascular disease: epidemiology and prognostic significance

If ECG changes are to be taken as a good marker of vascular disease, we must examine the range of ECG abnormalities in the population and relate this to underlying vascular disease. Surprisingly, there has been only one published review looking at the prevalence and prognostic significance of ECG abnormalities (Ashley, Raxwal & Froelicher, 2000). The authors of this paper prefaced their review with the statement "Despite its ubiquity, the value of using the resting 12-lead ECG as a screening test for CVD in asymptomatic patients has never been convincingly demonstrated" (Ashley, Raxwal & Froelicher, 2000, p. 7). The authors went on to review the literature from 1966 through to 1999 looking at prevalence of and prognostic importance of ECG abnormalities. Their review encompassed a broad-ranging group of important epidemiological studies, including the Framingham Heart Study, the Copenhagen City Heart Study, UK studies and the Multiple Risk Factor Intervention Trial (MRFIT), amongst others. There were many methodological issues including problems comparing demographically diverse populations, the many varying exclusions in studies and indeed the variety of methods of actually analysing ECG data.

One of the major problems identified by this review is that there are few studies published showing the prevalence of ECG abnormalities in the very elderly, this despite the fact that all ECG abnormalities increased in frequency with age. Most of

the data relate to younger ages, and in fact most of the prevalences quoted split the age into decades but group together all those individuals greater than 69 years old.

In fact, this review identified only three papers which specifically set out to look at ECG changes in the elderly: the Cardiovascular Health Study (Furberg et al., 1992) and two Finnish papers looking the prevalence of ECG abnormalities and their association with survival in the very old (Rajala et al., 1984; Rajala et al., 1985). Furberg et al. (1992) used the Cardiovascular Health Study, a study of risk factors in stroke and cardiovascular disease, to determine the prevalence of ECG abnormalities in adults age 65 years or older. They recruited 5210 people, 95% of whom were white and analysed their resting ECGs using the Minnesota coding. They specifically looked at 6 'major' ECG abnormalities: ventricular conduction defect, Q waves, LVH, ST segment depression, atrial fibrillation and 1st degree heart block. The frequency of the presence of one or more of these major abnormalities was compared in people with and without cardiovascular disease (as recorded by self-reporting of MI, angina or hypertension). The frequencies are shown in table 4.1 for men and women stratified by age group.

Table 4.1: Prevalence of ECG abnormalities stratified by age in the Cardiovascular Health Study

	Disease free		Disease	
Age	Men n (%)	Women n (%)	Men n (%)	Women n (%)
65-69	582 (10.5)	319 (16.0)	555 (25.8)	372 (37.9)
75-79	243 (20.2)	204 (27.5)	343 (39.4)	261 (52.9)
80-84	98 (17.3)	114 (39.5)	144 (38.9)	127 (55.1)
85+	38 (31.6)	61 (45.9)	49 (38.8)	36 (61.1)

The authors concluded that ECG changes were very common in the elderly, and there were significant gender differences noticed for all ECG abnormalities except LVH. They also reported that ECG abnormalities increase in frequency with age and that ECG abnormality was more common in people with cardiovascular disease.

Rajala et al. (1984) published prevalence data for ECG abnormalities in a very elderly group, those age 85 and over, living in a large Finnish city. They managed to study the ECG in 83% (559 out of 674 possible subjects) of the entire population of 85+ year olds. They used the Minnesota coding. The ECG in this group was entirely normal in normal in only 4% of cases. The frequencies of ECG abnormalities found in this study are presented in table 4.2.

Table 4.2: Prevalence of ECG abnormalities in a group of over 85 year olds

	Prevalence of abnormality (%)	
ECG abnormality	Male	Female
Q-waves	32.3	17.8
ST depression	31.3	45.2
T inversion	43.3	55.4
A-V conduction defect	15.2	9.1
Ventricular conduction defect	28.3	13.7

This group went on to show that ECG changes were associated with predictive value with respect to survival, with the highest rates of survival being present in those with normal ECG or only minor abnormalities (Rajala et al., 1985).

Both the studies mentioned above reported roughly similar findings very much in line with the results presented by Ashley, Raxwal & Froelicher (2000). Importantly, ECG changes become increasingly more common as age rises and ECG changes are

more common in men, which should be predicted by the fact that vascular disease is more common in men.

More recent papers attempting to look at prevalence of and prognostic significance of ECG abnormalities have once again failed to look at the most elderly. For example, Larsen et al. (2002) looked at a group of people from Copenhagen. The age range examined in this paper was 24 to74. In the oldest age group, from 65 to 74, there were 750 men (from a total of 5243) and 748 women (from a total of 6391). Similarly, de Bacquer et al. (2000) published a paper describing four very large epidemiological studies of ECG abnormalities in a Belgian population. Spanning 30 years, there were a total of 47 358 subjects and once again the age range studied was 25 to 74. Of 34 731 men, there were only 962 people in the oldest age group from 65-74 and of the12 637 women, only 718 were in this oldest age group. In other words there is a real lack of good data describing the range of abnormalities that might be expected to be seen in a cohort of 80-year olds.

De Bacquer et al. (2000, p. 629) state "The ECG has been widely described in medical reports as a useful diagnostic tool for assessing "silent" heart disease." This statement is not referenced, however. Whilst it is part of perceived medical wisdom that ECG changes reflect underlying heart disease, this is backed up by the results reported by De Bacquer et al. (2000); major ECG changes (defined as ST segment depression, T wave inversion, complete or second degree atrioventricular block, complete left or right bundle branch block or frequent premature beats based on Minnesota coding), were strongly associated with coronary artery disease, OR=9.35, 95% CI 8.5-10.3. A similar significant association was also found for Q waves, ST segment depression, T wave inversion, the presence of atrio-ventricular block and ischaemic ECG findings.

Further evidence linking ECG changes to underlying vascular disease comes from mortality data. Importantly, Ashley, Raxwal & Froelicher (2000) conclude that ECG abnormalities carry an adverse prognostic risk of mortality; for example LVH has a

5-year mortality of 33% in men and 21 % in women. De Bacquer et al. (1998) reported on the Belgian inter-university research on nutrition and health study. With an initial sample of 11,048 subjects, 99% of these subjects were followed up for at least 10 years. They found an increased relative risk for all cause mortality for people with major ECG abnormalities, this result being present in men and in women. In addition, the presence of any abnormality on ECG was associated with increased cardiovascular mortality (in men RR = 1.70, 95% CI 1.25-2.32; in women RR = 1.82, 95% CI 1.14-2.90). These data can be taken as direct evidence linking ECG changes to vascular disease, supporting the proposition that ECG changes can be taken as a marker of vascular disease.

Electrocardiographic changes and late-life cognitive function: a case-control study

Methods

This study looked at ECG changes and cognitive function in the LBC1921. The methodology used for the LBC1921 was described above in chapter I, part 2. To re-iterate, The LBC 1921 followed up, between 1999-2001, 550 surviving participants of the SMS1932 residing in the Edinburgh area. All were volunteers who lived independently in the community. They undertook a cognitive battery including repeating the original MHT test, MMSE, Raven's progressive matrices, logical memory and verbal fluency. The MHT scores at age 11 and age 80 were converted to IQ scores corrected for age in days. As part of the LBC investigation, a number of self-reported health states were recorded. These were the presence or absence of cardiovascular disease, cerebro-vascular disease, diabetes, neoplasia, hypertension and 'any other disease'. Each participant underwent a physical examination and 532 individuals (96.7%) had a 12-lead ECG performed.

Each ECG was analysed applying the 1982 version of the Minnesota coding (see below for description; Prineas et al., 1982). The data were then re-coded into 'normal' and 'abnormal' for the following ECG variables: axis, A-V conduction, ventricular conduction, ST depression, ST elevation, T wave, R amplitude. In addition, the ECGs were coded as 'normal' if entirely normal and 'abnormal' if there was any ECG abnormality present. The ECGs were recoded for abnormalities in the following 3 areas: conduction defect (where there was either AV or ventricular conduction defect), ischaemia (where there were ST, T or Q wave abnormalities) and LVH (where there was LVH by voltage criteria).

Methodology: a note on the Minnesota coding

The Minnesota coding was developed by Blackburn et al. (1960), and revised in 1982 (Prineas et al., 1982). It was designed as a tool to standardise the interpretation of ECG abnormalities for comparison in epidemiological studies. It gives rigid criteria based on electrical morphology from which codes are derived. These codes relate to changes in cardiac rhythm, as well as changes in Q-waves, T-waves, QRS duration, ST segment shifts and ventricular hypertrophy. These codes do not equate to clinical diagnoses, which must be inferred from the presence or absence of the coded abnormalities.

The Minnesota coding is not flawless. Firstly, no coding is 100% accurate, even when automated. The accuracy of manual interpretation of ECG abnormalities has been as high as 87.5% (Tuinstra et al., 1981). In the case of this study, the Minnesota coding was performed manually, with a second rater independently applying the coding to the same ECG, resulting in a significant inter-rater reliability (kappa values quoted above). Secondly, the coding does not take into account age or sex, which must then be accounted for in any statistical analyses. Nonetheless, the Minnesota coding is used in the majority of population based studies where ECG data are analysed (MacFarlane, 2000), an example of which includes the West of Scotland Coronary Prevention Study (West of Scotland Coronary Prevention Study Group, 1992).

Statistical analyses

Reliability of ECG analysis was tested using kappa scores. Fifty ECGs were re-assessed by an independent examiner. There is a good inter-rater reliability (kappa for axis = 1.0, $p<0.001$, kappa for ST depression = 0.547, $p<0.001$).

Differences in cognitive test scores were analysed for people with and without conduction defects, ischaemic changes and LVH on ECG. ANOVA was tested using independent t-tests. Difference in frequencies of ECG abnormalities was tested using

χ^2 tests. Binary logistic regression was used to test whether childhood mental ability was predictive of ECG change. The overall contribution of ECG changes to late life cognition was tested using general linear modelling.

Because of the sex differences that exist in cardiac disease, data were analysed separately for men and women.

Results

There were 532 (96.7%) people in the LBC who had an ECG performed (223 men, 309 women). There was no difference in the number of ECGs performed in each sex ($\chi^2 = 0.165$, p=0.213).

Possible differences in cognition between those who did and did not get an ECG during their LBC physical examination were explored. Table 4.3 shows the differences in MMSE, MHT age 11 and MHT age 80, Raven's and verbal fluency.

Table 4.3: Differences in cognitive test scores by ECG recording in LBC

	ECG performed				
	Yes		No		
Cognitive test	n	mean (SD)	n	mean (SD)	sig.
MMSE	531	28.2 (1.6)	17	26.9 (3.0)	p=0.09
MHT age 11	475	46.7 (11.9)	17	39.2 (13.9)	p=0.01
MHT age 80	527	59.4 (10.7)	14	52.0 (14.5)	p=0.01
Raven's	527	31.3 (8.7)	15	25.0 (9.6)	p=0.006
Verbal Fluency	529	40.2 (12.2)	16	34.4 (16.2)	p=0.07

The people who did not get an ECG in their LBC investigations had a lower MMSE, although this is just outside statistical significance. They did however have a significantly lower mental ability in childhood and a significantly lower IQ aged 80. Again, RPM and verbal fluency scores were lower in those who did not get an ECG, although these latter are outside statistical significance. These results are unlikely to have importantly biased the results in terms of ECG changes and cognitive decline. The numbers are small, though: only 18 people did not get an ECG.

Table 4.4 shows the frequency of ECG abnormalities expressed as percentages in people who participated in the LBC. To give an idea of "silent" ECG changes, table 4.4 displays the frequencies of ECG abnormality in those in the LBC with and without self-reported vascular disease. Overall in the whole group, only 34.0% had an entirely normal ECG.

Table 4.4: Percentages of ECG abnormalities in the LBC1921

	ECG abnormality	Vascular disease	No disease	χ^2	Sig.
Men	Axis	16.7	12.7	0.6	p=0.46
	A-V cond.	10.3	7.9	0.3	p=0.57
	Ventricular cond.	25.2	13.2	4.4	p=0.04
	Q-waves	27.2	10.7	7.9	p=0.005
	ST depression	20.0	9.9	3.37	p=0.07
	T wave	35.8	22.5	3.7	p=0.06
	LVH	12.3	2.9	4.7	p=0.03
	Any abnormality	82.2	68.4	5.4	p=0.02
Women	Axis	11.0	13.4	0.4	p=0.33
	A-V cond.	7.1	2.5	3.2	p=0.08
	Ventricular cond.	15.5	9.0	2.7	p=0.10
	Q-waves	10.5	5.0	2.8	p=0.09
	ST depression	18.4	5.9	9.3	p=0.002
	T wave	25.2	13.6	5.7	p=0.02
	LVH	13.0	6.9	2.7	p=0.10
	Any abnormality	65.0	47.2	9.6	p=0.002

The frequency of abnormalities was higher on the whole in those with self-reported vascular disease, although the difference did not always reach statistical significance.

Men were more likely to have any ECG abnormality present (χ^2= 23.0, p<0.001). This was also true of AF (χ^2=9.9, p=0.002), ventricular conduction defects (χ^2=6.3, p=0.01), q wave abnormality (χ^2= 18.0, p<0.001), T wave inversion (χ^2=7.2, p=0.007) and ST elevation (χ^2, p<0.001), conduction defect (χ^2=8.6, p=0.003) and ischaemic change (χ^2, p<0.001). However, there were no significant differences between men and women in frequencies of left axis deviation (χ^2= 0.17, p=0.68), A-V conduction defects (χ^2=3.6. p=0.06), ST depression (χ^2=0.70, p=0.4) or LVH (χ^2=0.34, p=0.56).

Is childhood mental ability predictive of ECG change?

This was analysed using binary logistic regression looking at ECG outcomes and age 11 mental ability. Table 4.5 shows the results.

Table 4.5: Binary logistic regression of ECG outcomes and age 11 IQ

	Odds ratio (95% C.I.)	Significance
Overall ECG abnormality	1.00 (0.99, 1.02)	p=0.68
LAD	1.01 (0.99, 1.03)	p=0.34
LBBB	1.02 (0.98, 1.05)	p=0.39
AF	1.01 (0.97, 1.04)	p=0.76
Q wave	0.99 (0.98, 1.01)	p=0.52
ST dep	1.00 (0.98, 1.02)	p=0.90
T wave	1.00 (0.99, 1.02)	p=0.92
LVH	0.98 (0.96, 1.01)	p=0.14

Mental ability age 11 is not associated with ECG change in later life.

Cognitive ability and ECG changes

The MHT scores at age 11 and age 80 were analysed in those with and without ECG changes. The raw MHT scores were corrected for age in days and converted to give an IQ type score (mean 100, SD=15). The results for IQ age 11 are shown in table 4.6A, and those for IQ age 80 are shown in table 4.6B.

Table 4.6A: IQ age 11 in different ECG categories

		Men			Women		
ECG change		n	Mean IQ Age 11 (SD)	Sig.	n	Mean IQ Age 11 (SD)	Sig.
LVH	Yes	32	98.5 (17.8)		48	99.4. (17.24)	
	No	133	99.7 (15.1)	0.69	204	101.0 (13.6)	0.49
Cond Defect	Yes	54	99.3 (15.8)		48	100.9 (16.0)	
	No	143	100.2 (15.4)	0.74	229	100.6 (13.9)	0.91
Ischaemia	Yes	89	98.9 (15.1)		75	101.0 (17.0)	
	No	89	99.8 (16.2)	0.70	183	100.5 (12.9)	0.81

Table 4.6B: IQ age 80 in different ECG categories

		Men			Women		
ECG change		n	Mean IQ Age 80 (SD)	Sig.	n	Mean IQ Age 80 (SD)	Sig
LVH	Yes	35	104.3 (14.2)		53	98.8 (17.2)	
	No	145	101.5 (14.2)	0.30	225	99.5 (14.1)	0.75
Cond Defect	Yes	61	101.0 (16.2)		53	98.0 (16.5)	
	No	158	102.2 (14.1)	0.59	252	99.3 (14.3)	0.55
Ischaemia	Yes	93	100.8 (13.8)		84	99.5 (16.1)	
	No	183	102.7 (12.9)	0.36	200	99.0 (14.3)	0.80

There were no differences in IQ at age 11 or at age 80 demonstrated in either men or women with ECG changes.

Next, the results on cognitive test scores (MMSE, RPM, logical memory and verbal fluency) were analysed in those with and without ECG changes. Men and women were again analysed separately. The result of these are shown in table 4.7, with 4.7A being for the men and 4.7B for the women.

Table 4.7A: Differences in cognitive test scores by ECG abnormality: men

		Ravens		MMSE		Verbal Fluency		Logical Memory	
ECG abnormality		n	Mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
LVH	Yes	35	34.8 (9.0)	36	27.7 (2.0)	36	41.4 (13.0)	36	34.2 (16.2)
	No	145	32.5 (8.6)	147	28.3 (1.5)*	147	39.9 (12.0)	147	31.6 (12.7)
Conduction defect	Yes	61	32.8 (8.0)	62	28.0 (1.6)	61	40.1 (13.6)	62	32.1 (12.0)
	No	160	32.7 (8.8)	160	28.2 (1.6)	160	38.0 (11.7)	160	32.5 (13.5)
Ischaemic Change	Yes	94	32.0 (8.0)	95	28.1 (1.5)	96	39.0 (12.2)	95	31.2 (12.0)
	No	102	33.4 (9.1)	102	28.2 (1.7)	101	40.3 (12.0)	102	32.7 (14.2)

* p=0.05

Table 4.7B: Differences in cognitive test scores by ECG abnormality: women

		Ravens		MMSE		Verbal Fluency		Logical Memory	
ECG abnormality		n	Mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
LVH	Yes	53	30.6 (8.9)	54	28.2 (1.7)	54	38.0 (10.9)	54	29.0 (13.3)
	No	225	30.5 (8.5)	147	28.4 (1.6)	226	41.5 (12.2)*	227	31.7 (12.6)
Conduction defect	Yes	52	29.8 (8.6)	53	28.0 (1.8)	53	35.6 (12.7)	53	32.1 (13.2)
	No	253	30.4 (8.7)	255	28.4 (1.6)	254	41.4 (11.9)**	255	31.1 (12.5)
Ischaemic Change	Yes	84	29.7 (8.8)	85	28.3 (1.8)	85	38.7 (11.6)	85	32.0 (12.5)
	No	200	30.7 (8.6)	202	28.3 (1.6)	201	40.3 (12.3)	202	30.7 (12.7)

* p=0.05 **p=0.001

Men with LVH have a lower mean MMSE score (p=0.05). The data were re-analysed, excluding people with a diagnosis of dementia and those with an MMSE of ≤24. There was now no difference in MMSE in any of the ECG categories. There were no differences in any of the other cognitive tests in any of the ECG categories.

Women with LVH had lower verbal fluency scores. This was also true for women with conduction defects. Although women with ischaemic changes on the ECG had lower verbal fluency, this did not reach statistical significance. Other ECG changes were not associated with verbal fluency and no ECG changes were associated with lower scores on the other cognitive tests.

Self-reported disease state, cognitive function and ECG changes

As part of the LBC investigation, a number of self-reported health states were recorded i.e. presence/absence of cardiovascular disease, cerebrovascular disease, diabetes, neoplasia, hypertension and "any other disease". The frequencies of ECG abnormality in each group were compared using the χ^2 test.

Table 4.8 shows that those with self-reported cardiovascular disease, cerebrovascular disease, diabetes and hypertension were more likely to have ECG changes. This is an important finding, as it means that the ECG changes may tend to reflect underlying cardiovascular disease (as can also be seen in table 4.4 where the prevalence of most individual ECG changes was shown to be higher in those with any self-reported vascular disease).

Table 4.8: Self-reported disease and ECG changes

Self-reported disease		ECG (n)		χ^2	Sig.
		normal	abnormal		
Cardiovascular	yes	11	75		
	no	149	221	25.9	p<0.001
Cerebrovascular	yes	5	35		
	no	175	313	9.1	p=0.01
Hypertension	yes	58	157		
	no	121	190	8.5	p=0.01
Diabetes	yes	4	22		
	no	177	329	4.2	p=0.04
Dementia	yes	1	2		
	no	179	348	0.001	p=0.98
'Other Vascular'	yes	16	24		
	no	163	326	4.6	p=0.10

Overall, ECG abnormality was present more frequently in people with self-reported vascular disease. The data in table 4.8 also imply that cardiovascular disease, cerebrovascular disease, hypertension, diabetes and peripheral vascular disease are all considered 'vascular disease'.

Cognitive test scores were compared in those with and without any self-reported vascular disease. Of the volunteers for the LBC, 342 (62.2%) reported one or more vascular disease and 204 (37.1%) did not report any disease. Data were missing in four (0.7%) cases.

Table 4.9 shows the raw cognitive test scores in people with and without vascular disease.

Table 4.9: Differences in cognitive test scores by self-reported vascular disease in LBC

	Self-reported vascular disease				
	Yes		No		
Cognitive test	n	mean (SD)	n	mean (SD)	sig.
MMSE	341	28.2 (1.8)	203	28.2(1.6)	p=0.86
MHT age 11	313	46.3 (11.8)	177	46.6 (12.6)	p=0.78
MHT age 80	338	59.3 (10.7)	200	59.1 (11.1)	p=0.85
Raven's	339	31.3 (8.4)	200	31.0 (9.5)	p=0.71
Verbal Fluency	340	39.0 (12.5)	201	41.6 (11.9)	p=0.02

People with self-reported vascular disease have lower scores on verbal fluency than those without. There is no difference in the other cognitive tests.

An important question is to answer whether ECG changes truly reflect underlying vascular disease. We have seen in table 4.6 that men with ischaemic ECG change on ECG have a lower MMSE and that women with conduction defects and LVH have lower scores on verbal fluency. We have also seen that ECG changes are more frequently found in people with self-reported vascular disease (tables 4.4 and 4.8) and that verbal fluency is lower in people that reported vascular disease (table 4.9). In order to attempt to look at the relation between ECG changes and self-reported vascular disease further, the cognitive test scores were analysed in only those who did not report vascular disease. In other words, clinically silent ECG changes were examined, and the results of cognitive test scores are shown for this group in tables 4.10 and 4.11. The results are shown in table 4.10A and 4.11A for men and 4.10B and 4.11B for women.

Table 4.10A: IQ age 11 in different ECG categories in people without self-reported vascular disease

		Men			Women		
ECG change		n	Mean IQ Age 11 (SD)	Sig	n	Mean IQ Age 11 (SD)	Sig
LVH	Yes	8	97.9 (15.3)		18	103.1 (19.2)	
	No	52	102.1 (15.4)	0.48	84	99.7 (13.5)	0.48
Cond Defect	Yes	12	104.9 (18.5)		13	104.2 (15.5)	
	No	51	100.8 (15.2)	0.42	95	100.2 (14.5)	0.59
Ischaemia	Yes	22	100.5 (15.7)		20	103.4 (17.2)	
	No	39	101.3 (15.8)	0.84	46	99.5 (13.9)	0.28

Table 4.10B: IQ age 80 in different ECG categories in people without self-reported vascular disease

		Men			Women		
ECG change		n	Mean IQ Age 80 (SD)	Sig.	n	Mean IQ Age 80 (SD)	Sig
LVH	Yes	18	103.1 (19.2)		21	102.5 (14.0)	
	No	84	99.7 (13.5)	0.48	93	98.1 (14.1)	0.21
Cond Defect	Yes	13	102.6 (17.6)		14	98.9 (17.2)	
	No	95	100.2 (14.5)	0.59	106	98.5 (14.4)	0.94
Ischaemia	Yes	20	103.4 (17.2)		23	101.3 (12.9)	
	No	84	99.5 (13.9)	0.28	93	97.9 (15.0)	0.32

In those volunteers in the LBC who did not report vascular disease, there were no differences in IQ age 11 or at age 80 when those people with ECG changes were compared to those without.

The results of Raven's, MMSE, logical memory and verbal fluency are shown in table 4.11. Men with ECG changes did not score differently to those without ECG changes (table 4.11A). There was a suggestion that those with ischaemic change had lower verbal fluency scores, but this was just outside statistical significance (p=0.08). Women with conduction defect on ECG had lower verbal fluency scores when compared to those with normal ECG. There were no differences in any of the other cognitive test scores in any of the ECG categories (table 4.11B).

Table 4.11A: Differences in cognitive test scores by ECG abnormality: men without self-reported vascular disease

		Ravens		MMSE		Verbal Fluency		Logical memory	
ECG abnormality		n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
LVH	Yes	9	32.8 (8.7)	9	27.7 (1.6)	9	45.8 (10.5)	9	38.0 (18.6)
	No	59	36.4 (9.7)	60	28.5 (1.4)	59	41.1 (11.3)	60	31.4 (12.7)
Conduction defect	Yes	16	32.8 (9.0)	16	28.9 (1.2)	16	43.8 (15.1)	16	34.6 (12.9)
	No	59	36.7 (7.4)	60	28.2 (1.5)	59	40.7 (10.8)	60	32.2 (13.4)
Ischaemic Change	Yes	24	32.8 (6.5)	25	28.4 (1.0)	25	38.0 (10.6)	25	31.0 (11.1)
	No	46	33.5 (9.8)	46	28.3 (1.7)	45	43.0 (11.7)	46	32.9 (14.6)

All results p = NS

Table 4.11B: Differences in cognitive test scores by ECG abnormality: women without self-reported vascular disease

Ravens		MMSE		Verbal Fluency		Logical Memory		
ECG abnormality		n	mean (SD)	n	mean (SD)	n	mean (SD)	n	mean (SD)
LVH	Yes	21	31.9 (7.9)	22	28.5 (1.0)	22	42.1 (12.2)	22	32.2 (15.2)
	No	93	29.2 (9.5)	94	28.2 (1.6)	93	42.3 (12.2)	94	31.7 (12.4)
Conduction defect	Yes	14	29.1 (11.6)	14	27.6 (1.8)	14	35.6 (14.6)	14	34.1 (13.8)
	No	106	29.6 (9.3)	108	28.3 (1.5)	107	42.9 (11.4)*	108	31.5 (12.8)
Ischaemic Change	Yes	23	27.0 (7.9)	24	28.2 (1.8)	24	40.9 (12.0)	24	31.6 (12.0)
	No	93	30.1 (9.8)	94	28.2 (1.5)	93	42.6 (12.1)	94	31.7 (13.3)

All results p=NS except *p=0.03

Overall contribution of ECG changes to late life cognitive ability: general linear modelling

The aim of this analysis was to test the hypothesis that ECG changes are associated with cognitive decline across the life-span. ANOVA was measured using general linear modelling. The dependent variable was IQ age 80 corrected for age in days. Sex was entered as a fixed factor and IQ age 11 as a co-variate. ECG changes were entered as co-variates. Interactions were assessed between ECG abnormalities and sex. Analyses were repeated in people without self-reported vascular disease to assess the contribution of silent ECG changes.

The results are shown in table 4.12.

Table 4.12: Estimated marginal means of IQ age 80 after controlling for ECG changes, sex and IQ age 11

		Estimated mean IQ age 80 (95% CI)	
ECG change		Whole group	Self-reported vascular disease excluded
LVH	Yes	102.4 (100.0 – 104.9)	103.7 (99.2 – 108.2)
	No	99.7 (98.5 – 101.0)	99.3 (97.4 – 101.1)
Conduction defect	Yes	99.4 (97.2 – 101.6)	100.0 (95.6 – 104.3)
	No	100.3 (99.1 – 101.4)	99.8 (97.9 – 101.7)
Ischaemia	Yes	99.6 (97.8 – 101.3)	100.6 (97.1 – 104.0)
	No	100.4 (99.0 – 101.8)	99.1 (97.0 – 101.2)

As can be seen from the estimated marginal means, for the whole group there were no main effects for any of the ECG changes on overall contribution to IQ age 80. For ventricular hypertrophy, $F = 3.7$, $p = 0.06$; for conduction defect $F = 0.49$, $p = 0.48$; and for ischaemia $F = 0.55$, $p = 0.46$. There was no interaction between sex and ventricular hypertrophy ($F = 0.22$, $p = 0.64$), sex and conduction defect ($F = 0.32$, $p =$

0.58) or sex and ischaemia ($F = 0.11$, $p = 0.75$). Similarly, when the analyses were repeated in those without self-reported vascular disease (i.e. where ECG changes were 'silent') there were no main effects on ECH changes and IQ age 80 and there were no interactions between sex and ECG changes.

Childhood mental ability, vascular risk and late-life cognition: discussion

The cause of cognitive impairment, in particular AD, is not known. Chapter II of this thesis demonstrated that mental ability in childhood is associated with increased risk of vascular dementia. Exactly how this occurs is not automatically clear, but data from the midspan-SMS collaboration (Starr et al., 2004; Taylor et al., 2003; Hart et al., 2004) link childhood mental ability to vascular factors such as elevated mid-life blood pressure, smoking cessation and atherosclerotic disease.

Chapter I of the thesis outlined the wealth of published literature detailing possible links between vascular disease and cognitive impairment. The data examined and presented include epidemiological studies exploring vascular risk factors and cognitive function. Importantly, autopsy data shows the ubiquitous presence of both Alzheimer's and vascular pathology in the brains of individuals who have dementia. Worryingly, the condition of VaD cannot always clinically be distinguished from AD, although in-depth neuropsychological assessment may be able to add to clinical diagnostic accuracy. A broad conclusion of this review of literature was that AD (and cognitive impairment) may have a significant vascular component to its aetiology. It was impossible to conclude on specific mechanisms or indeed make anything more than hypotheses over causality in the vascular links to AD.

From this stand-point, I have described a study looking at ECG changes and cognitive function in a group of relatively healthy volunteers, the LBC. This topic has not previously been extensively studied. I set out to examine the hypothesis that changes recorded on the ECG represent a marker of 'vascular' disease and as such should be associated with impaired cognitive function. The results of this study are discussed below.

ECG changes and mental ability age 11 and age 80

One of the main cognitive measures used in the LBC was the MHT. This gave a measure of IQ, or general mental ability at approximately age 80 and was important because it could be compared to the same measure of mental ability measured at age 11. Binary logistic regression was used to study if mental ability age 11 predicted ECG changes recorded on ECG at almost age 80. There was no association demonstrated between mental ability age 11 and ECG changes in late-life.

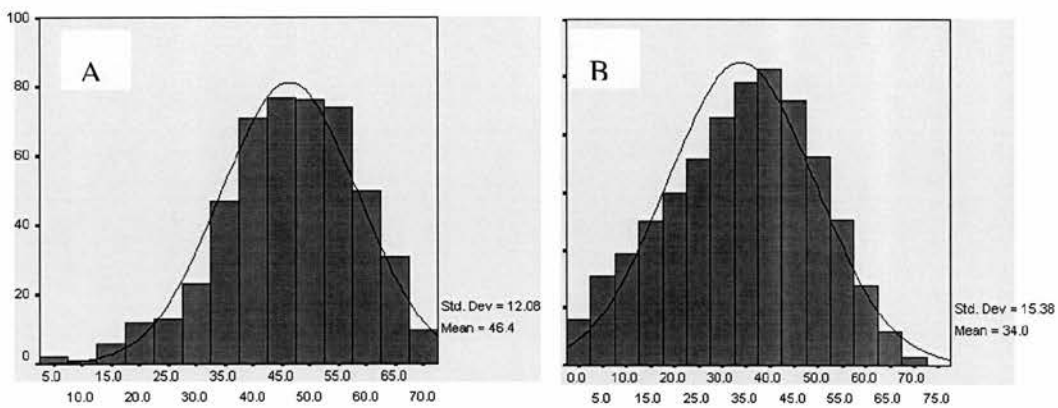
On the surface, this lack of association may be taken to mean that the link between mental ability in childhood and increased risk of dementia and cognitive decline is not mediated through a vascular mechanism. However, before drawing this conclusion, several factors must be taken into account. These may include characteristics both of the population sampled and the cognitive test used, and will be discussed below.

Possibly a more important result to look at is the degree of cognitive change across the life-span, from age 11 to age 80. The differences in IQ at these ages in people with and without ECG changes was examined and presented in table 4.6 (A and B). There were no significant differences. Similarly, ECG changes were not associated with IQ age 80 in general linear modelling (table 4.12) This could lead to the conclusion that vascular disease is not associated with cognitive change across the lifespan. As ever, one must consider other factors prior to accepting this conclusion.

The characteristics of the volunteer population sampled mean that their starting point was that of an elite group of healthy elders. In other words, they started off from a higher cognitive platform and were almost certainly more physically fit than the general population. Thus any contribution of vascular disease to poorer cognition will have been under-estimated by this selection bias.

The test characteristics may also have contributed to the finding of no link between ECG changes and mental ability age 11 or change between age 11 and age 80. Figure 4.1 demonstrates a histogram for (A) the LBC and (B) the MHT scores from the entire Scottish Mental Survey.

Fig 4.1: Histogram of MHT scores: A – LBC, B – whole SMS



As can be seen from these histograms, the LBC had MHT scores that were negatively skewed, with a higher mean MHT score and a lower standard deviation than the entire SMS1932 population. It may be that there was not enough variability within these test results to be able to predict expression of ECG changes in a population who, if they had disease, must by definition have had mild disease. More likely, though, is that the LBC represent an elite cohort. As such, even those with vascular disease almost certainly have mild disease, or have different expression of disease. Hence any difference in scores between those with and without vascular disease and ECG changes will have been underestimated.

The characteristics of the cognitive test used are also vital. The fact that there appears not to be a relationship between ECG changes and general intelligence (in this case measured by MHT and Raven's) is in keeping with the established view of published

literature. It is accepted that there is little link between performance on standard tests of intelligence and tests of 'frontal lobe function' which are often impaired in vascular dementia (Duncan et al, 1997; Damasio, 1985). Sachdev & Looi (2003) in their systematic review concluded that there were insufficient data to draw conclusions on the utility of results of tests of general intelligence in distinguishing AD and VaD.

There does not appear to be a link between childhood mental ability and ECG changes. If there is a true vascular link between lower childhood mental ability and late-life cognitive decline, this may question the validity of accepting ECG changes as a marker of cardiovascular disease. (This topic will be further explored later in this chapter). Alternatively, it may mean that the link between lower childhood mental ability and late-onset dementia is not caused by the adoption of 'risky' health behaviours as might lead to excess vascular risk. The precise mechanism of how lower mental ability in childhood might act as a risk factor for later life dementia remains elusive.

ECG changes and other tests of cognition

There are important sex differences in the expression of cardiovascular disease. As a result, the cognitive data were looked at separately in men and in women. Men with LVH but not ischaemia or conduction defect had a significantly lower mean MMSE (table 4.7A). This amounted to a very small difference – the mean score was 27.7 (2.0) in those with and 28.3 (1.5) in those without. Prior to accepting this result there are several things to be considered. Firstly, this difference was present only for men and was not present in women. There are no immediately obvious reasons as to why this might be. This, coupled with the fact that the statistical level of significance of the t-test was $p = 0.05$ i.e. just at the traditionally accepted levels of significance, means that type I error may have caused this result by chance. Secondly, there were

no differences in MMSE for men or for women in any of the other ECG categories compared to normal (table 4.7, A & B). This might lead one to question the veracity of this result, that men with LVH have a lower MMSE, as it is not present in any of the other ECG categories. However, as discussed in part 1 of this chapter, there is not necessarily a single pathological pathway leading to vascular mediated brain damage. LVH on ECG is commonly accepted as a result of hypertension, which has not been well controlled over many years and in fact represents end-organ damage. Perhaps then it is hypertension that is the important factor and leads to vascular damage in ways other than macro-vascular ischaemia.

The mean MMSE was 0.6 points lower in men with LVH when compared to those without LVH. The clinical significance of this lower MMSE may be questioned. In considering whether this is a true result or a result thrown up by chance, a comparison to previous studies is vital. The Rotterdam study reported a remarkably similar result: people with ECG changes of previous myocardial infarction had an MMSE lower by 0.7 of a point (Breteler et al., 1994). In the Caerphilly cohort (Elwood et al., 2002), there was a 0.3 point lower MMSE in people with probable ischaemia on ECG. The magnitude such a drop in MMSE seems small. This deficit in MMSE may not have a functional impact on a particular individual, but on a population level this decreased MMSE could have a more significant effect. A 0.6 difference represents 33% of one standard deviation.

There were significantly lower scores on verbal fluency in women with ECG changes of conduction defect and ECG changes (table 4.7B). Women with ischaemic ECG changes also had a lower verbal fluency score, although this is just outside of statistical significance with a $p = 0.06$. It is less likely that these results represent type I error. There is a lower score in verbal fluency in all three ECG categories. However, it remains unclear why men with ECG changes have no reduction in their verbal fluency score.

It is of some interest that in this sample it seems only verbal fluency scores and not other cognitive tests that are lower in people with ECG changes. Verbal fluency is said to be a test of executive function (Lezak, 1995), which is often ascribed to be a frontal lobe function e.g. attention, planning, sequencing (Ferris et al., 1997, Mohs et al., 1997). Impaired executive function is typically considered to be the earliest and most prominent cognitive change in VaD (Desmond et al., 1999). Deficit in executive function is quoted as useful in distinguishing AD and VaD (Sachdev & Looi, 2003). Impaired executive function is hypothesised to be a disruption in frontosubcortical circuits, which are particularly vulnerable to white-matter lesions and lacunae caused by small-vessel disease (O'Brien et al., 2003; Looi & Sachdev 2000). Unfortunately, verbal fluency and ECG changes were not assessed in either the Caerphilly cohort or in the Rotterdam study, and so it is difficult to place the result presented in this thesis in the context of previous literature.

Do ECG changes represent a marker of vascular disease?

This is quite possibly the most important question in this section of the thesis. In interpreting the results section, I have made the assumption that ECG changes do represent a marker of vascular disease. This section challenges this assumption.

This study has shown ECG changes to be very common, even in a group of healthy volunteers such as this group, the Lothian Birth Cohort. Overall, 66% of all people who participated in the LBC had an abnormal ECG. This contrasts with 63% of the LBC who self reported any vascular disease or a major risk factor. In table 4.4, data show that most ECG changes are more frequent in people who self-report vascular disease. Table 4.8 shows that subjects with cardiovascular disease, cerebrovascular disease, hypertension and diabetes are more likely to have an abnormal ECG. In this respect, an abnormal ECG can be considered to be a marker of vascular disease. It is

important, though, to address exactly how much ECG abnormalities can be considered to represent a marker of vascular disease.

Table 4.13: 2x2 table to calculate specificity and sensitivity of ECG changes for self-reported vascular disease in the LBC

		Self reported vascular disease	
		Yes	No
ECG	Abnormal	239	110
	Normal	90	89

Table 4.13 shows a 2x2 table to calculate specificity and sensitivity of ECG changes for self-reported vascular disease in the LBC. The specificity was 44.7% and the sensitivity was 72.6%. Sensitivity refers to the proportion of people with disease who have a positive test result. Here at 72.6%, this means that a normal ECG makes cardiovascular disease unlikely. The specificity refers to the proportion of people without disease who have a negative test result. In this respect, there was an important false negative rate. However, vascular disease has a high prevalence in the general population. Therefore, looking at the positive predictive value may be a more useful way of assessing whether an abnormal ECG is likely to represent vascular disease. Positive predictive value here was 68.4%. This means that an abnormal ECG, in this case a positive test, in the context of a high prevalence disease is most likely to be indicative of true disease.

Another important aspect of the question as to whether ECG changes represent vascular disease is that the LBC used self-reported vascular disease and did not corroborate this with the volunteers' GP or by detailed clinical evaluation. Relying on a self-reported history of vascular disease may underestimate the effect of covert vascular disease on AD (Stewart, 1998). However, the LBC volunteers were a healthy, cognitively intact group who are unlikely to have over or under-estimated the rate of vascular disease. This remains an assumption.

Another piece of evidence to be considered was shown in table 4.9; people with self-reported vascular disease had lower scores on verbal fluency. Women with ECG changes had lower verbal fluency scores. This implies a relation between abnormal ECG and vascular disease.

The relationship between vascular disease and ECG change is made more difficult to interpret because it is difficult to assess the impact of silent subclinical vascular disease. To explore the impact of silent ECG changes on cognition, data were analysed only in those who did not self-report vascular disease. In this group, there were no differences in any of the cognitive test when those with ECG changes were compared to those without. This may be taken to imply that vascular disease is important in cognitive impairment and that ECG changes are thus a poor marker of vascular disease. However, it may be that there is a 'dose-response': ECG abnormality in those without vascular disease may represent pre-clinical disease that has not yet had time to lead to detectable decline in cognitive function.

A summary of ECG changes and cognitive function

This thesis suggests that childhood mental ability has an important relation to risk of cognitive decline. This chapter has explored a possible mechanism, namely that an effect on cognitive decline is mediated through vascular mechanisms. Much plausible biological evidence (especially autopsy studies) linking vascular disease to acquired cognitive impairment supports this (see chapter I). I have presented a study looking at ECG changes and cognitive function in a group of healthy volunteers, the Lothian Birth Cohort.

I demonstrated that even in this healthy group of 'elite' elders, ECG changes were associated with poorer scores on cognitive tests. In particular this was on the MMSE for men and verbal fluency for women, in line with published literature (Breteler et

al., 1994; Sachdev & Looi, 2003). This implies that vascular disease is an important determinant of cognitive 'wear and tear' and that this may be evident prior to any clinically apparent cognitive decline. This conclusion hinges on the assumption that ECG changes are of course markers of vascular disease. Evidence that this is the case was presented in that ECG changes are more common in the people in the LBC who self-reported vascular disease, and that clinically 'silent' ECG changes (with less vascular burden) are not associated with lower cognitive test scores.

I did not demonstrate a link between IQ measured at age 11, or at age 80, and ECG abnormality. This may have been predicted by other work suggesting that general test of intelligence were not affected by vascular disease (Sachdev & Looi, 2003). This does not preclude a vascular mechanism of action to explain the fact that lower mental ability in childhood seems to be linked to late-onset dementia diagnosed in late life.

Chapter V. Childhood mental ability and late-onset dementia: general discussion

This thesis has presented studies of childhood mental ability and late-onset dementia. The Scottish Mental Survey of 1932, which gave a valid measure of childhood mental ability (the MHT score), made this possible. The hypothesis that lower childhood mental ability is associated with a greater risk of dementia was examined in chapter II. Data from a matched case-control study generally support this hypothesis, but only for the vascular sub-type of dementia: for every 10-point increase in a test of mental ability (about 2/3rd of a standard deviation change) there is approximately a 40% reduction in the odds ratio of being diagnosed with vascular dementia.

The relation between AD and childhood mental ability in this case-control study was very complex. There was no association demonstrated between AD and childhood mental ability. Methodological issues might partially explain this finding. The cases were all identified from dementia case registers in secondary and tertiary settings in Edinburgh. The cases attending one of these tertiary settings, the Lothian Memory Treatment Centre, had higher than average MHT scores. This does not fully explain the lack of association, as MHT scores for people with AD were similar despite the source of case identification. More studies are required to determine the real relationship between childhood mental ability and late-onset AD.

This thesis demonstrated a major association between migration and childhood mental ability. In this study, population controls were identified from the register of births, deaths and marriages. Descriptive statistics showed that on the whole, migrators had a greater MHT score than their birth regions' average. Thus comparing a migrating population (cases) to a more static population (controls) would have tended to imply an increasing risk of dementia with increasing mental ability. The effect of migration was known about: Whalley et al. (2000) showed that in the

Aberdeen Birth Cohort, those who had migrated out of Aberdeen (n = 735) had a mean MHT score of 37.4 (95% CI 36.3-38.4) whilst those subjects traced to Grampian (n = 1082) had a mean MHT score of 34.2 (95% CI 33.3-35.0, $p<0.001$). This thesis confirms the major effect of migration and suggests that the effect may be larger than previously thought. This has ramifications for future studies of intelligence across the lifespan: effects of migration must be adequately controlled for in such studies.

The underlying mechanism as to how lower childhood mental ability leads to increased risk of dementia is not entirely clear. Of great interest is the growing body of evidence linking vascular risk factors to AD. This thesis was able to use ECG changes as a mark of vascular disease and analyse whether ECG changes were associated with cognition. Chapter IV described this study in a group of healthy volunteers. There was no relation between MHT score at either age 11 or age 80 and ECG changes. This can be interpreted as implying that the link of lower mental ability and dementia might be mediated through non-vascular mechanisms. However, the MHT is a test of general intelligence and as such may not be particularly affected by vascular disease (Sachdev & Looi, 2003). This thesis did demonstrate that even in a group of healthy volunteers ECG changes were associated with poorer performance on some tests of cognition (MMSE in men, and verbal fluency in women). This adds further evidence to support the position that vascular factors are an important determinant of cognitive decline and dementia.

Having a valid measure of childhood mental ability gave the unique opportunity to study the utility of the estimation of pre-morbid mental ability in dementia. Diagnosing dementia requires evidence of cognitive decline. Some people continue to score highly on cognitive testing despite the presence of important dementia. Comparing current cognitive function to an estimate of pre-morbid intellectual level may allow the demonstration of decline required to diagnose dementia. The test used most commonly in clinical practice to estimate pre-morbid mental ability is the National Adult Reading Test (NART). In chapter III, this thesis presented a study

confirming the retrospective validity of the NART across a 69 year interval: the NART (measured at about age 80) was correlated with MHT score age 11. Almost 50% of the variance in a test of psychometric intelligence measured in childhood is explained by the NART administered in late life. This thesis comprehensively confirms the retrospective validity of the NART as a measure of pre-morbid ability across virtually the whole lifespan in a way that even the NART's original authors were unable to do.

The NART is considered a 'hold' test. That is, NART scores should not be affected by the neurological deficits of dementia. A question still remains about whether NART scores do in fact decline in dementia. A case-control study in chapter III compared NART scores in a group of people with dementia to a healthy control group. The group with dementia did score lower on their NART scores but also scored lower on MHT. When NART scores were controlled for MHT, there was no longer a difference in NART scores between the two groups. An interpretation of these results would be that the NART remains a valid test of pre-morbid ability even in mild-moderate dementia.

Possible implications for future work from data presented in this thesis are now discussed.

Future work suggested by this thesis

Childhood mental ability and late-onset AD

In chapter II of this thesis, data presented show a link between childhood mental ability and late-onset dementia. This is only for the vascular sub-type of dementia: no association between AD and childhood mental ability was demonstrated. This finding conflicts with published literature, notably from the Aberdeen Birth Cohort data (Whalley et al., 2000) and the Nun Study (Snowdon et al., 1996), which both suggest an increased risk of Alzheimer's disease and dementia in those with lower mental ability in early life. As discussed above, there may be methodological issues in relation to a case-control study which partially explain the findings of this thesis. In particular, selection bias in both cases and control groups may have had an important effect.

It may be that another type of study is required to examine the hypothesis that lower childhood mental ability is a risk factor for AD in later life. The first type of study would be a prospective cohort study. The Lothian Birth Cohort 1921 (LBC1921) would allow such a study to be performed. The cohort could be re-examined for incident dementia and could repeat neuropsychological testing. This will allow analyses to be performed to look at the overall contribution of childhood mental ability to cognitive decline. A big advantage of this approach is that the LBC1921 is a well characterised cohort with good data on factors such as socio-economic status, health status and physical function as well as neuroimaging. There are also disadvantages to this approach: the cohort is ageing and there is a great deal of attrition of cohort subjects. Therefore, this may under-estimate the contribution of childhood mental ability to AD. Other disadvantages are that this would be a complex and expensive study to perform. Nonetheless, this would be a very important study within the field of cognitive ageing.

The Scottish Mental Survey was repeated in 1947 for children born in the calendar year 1936. A prospective cohort with several waves of repeat testing of subjects born

in 1936 – including examination for incident dementia – would again be a very exciting cohort study. However, this approach would possibly take a long time to accumulate sufficient people with incident dementia; such a cohort would have volunteers currently (2006) age 70 and they would be healthy individuals at the inception of the cohort. Such a cohort could provide vital data including imaging and details about disease history in particular vascular diseases so that the vascular contributions to dementia and AD could be assessed.

A prospective cohort study with repeated measures of cognitive test scores looking at incident dementia would allow a more precise timing of the onset of dementia. Childhood mental ability may have on effect on age at diagnosis of dementia and on rate of cognitive change, both before and after diagnosis of dementia. If such a cohort study could be coupled to a pathological examination of brains at post-mortem, invaluable data would be generated. This would especially allow the role of vascular disease in Alzheimer's disease to be evaluated further.

Another possible study would be to treat the entire Scottish Mental Survey 1932 as a retrospective cohort. People who were diagnosed with dementia could be compared to those who do not have this diagnosis. Data would need to be linked to central databases of diagnostic codes and health records, taking into account mortality statistics. This research study would be massive and would tend to under-estimate dementia prevalence for two reasons: it would include people who had died prior to the age when they would be at risk of late-onset dementia and diagnostic coding tends to only include primary causes for seeking medical help. For example, if someone with dementia dies of pneumonia, then often the dementia is not recorded. The great benefit of this study would be size: 87,498 people took part in the SMS1932. This approach would also minimise the effect of migration as cases with dementia (if ascertainment was acceptable) would be compared to the entire population, so both cases and controls would contain individuals who had migrated within Scotland. Indeed, census data could identify individuals who had migrated and this could be controlled for in analyses. Socio-economic data would be basic and

other risk factors for dementia would be difficult to categorise. However, this study would go a long way to answering the question about the role of childhood mental ability in risk of dementia, AD and VaD.

This thesis has implications for future studies of intelligence and cognitive change. Although the effect of migration on mental ability is known, the magnitude of this effect may have been underestimated. Future studies of cognitive decline should adequately control for migratory status to attempt to avoid the bias caused by this.

Vascular factors, dementia and childhood mental ability

Further work should be aimed at assessing the burden of vascular disease on cognitive decline. Vascular disease is a very broad concept.

If ECG changes are associated with cognitive impairment via a vascular mechanism, then it would be hypothesized that ECG changes will be associated with ischaemic lesions and/or white matter lesions on brain imaging. An important study will be to see if there is a relation between ECG abnormality and CT/MRI brain abnormality, and how these relate to cognition. This should be possible as many of the volunteers for both the ABC1921 and the LBC1921 have had their brains imaged.

It would be interesting to look at 'silent' ECG abnormalities as a marker of pre-clinical cognitive decline. It would be hypothesized that people with ECG abnormalities should show more cognitive decline, especially on verbal fluency. This could be studied in two ways. Firstly, the LBC could be retested to see if there is a change in people with ECG changes. The development of new ECG changes (implying new, or progressive, disease) and its relation to cognitive change would be very enlightening. Secondly, as the LBC ages, more and more of its subjects will be diagnosed with dementia. A case-control study examining ECG changes as a risk factor for incident dementia would be an important piece of work.

The estimation of pre-morbid ability in dementia

The results presented in this chapter III of this thesis have implications for future studies and for clinical practice. It is evident that childhood ability may be a very important determinant in many aspects of cognitive neuroscience. Any differences in these cognitive functions between people with dementia when compared to people without may simply reflect the underlying individual differences in mental ability. The NART is a robust estimate of prior ability in both healthy populations and in people with mild-moderate dementia. A practical implication of this is that future studies may well be able to use the NART (rather than an actual measure of prior ability) as either a co-variable or as a measure on which to match for in a case-control study.

The NART is an estimate of pre-morbid intelligence, and gives a guide to probable pre-morbid level of function. This is compared to actual measured function to give a likely estimate of cognitive decline. It has been suggested that cognitive change at any point in time can be estimated by the NART-Raven difference (Davis et al., 2000; Freeman & Godfrey, 2000). Deary, Whalley & Crawford (2004) were able to explore the criterion validity of this approach by correlating estimated cognitive change with actual measured cognitive change. Using linear regression they obtained measures of actual life-time change (MHT age 11 – Raven age 78) and estimated life-time cognitive change (NART age 78 – Raven age 78). The estimated cognitive change correlated with actual cognitive change $r = 0.658$ ($p < 0.001$). The authors concluded that this approach, which takes only 30 minutes to administer, gives an 'instantaneous' estimate of a life-time's cognitive change, and that this "gives impetus to researchers to use the NART-Raven difference…to generate individuals' cognitive change scores" (Deary, Whalley and Crawford, 2004, p. 118). The authors admit that the sample they used (87 healthy elderly individuals) mean that the result cannot be generalised, and to be of practical use normative data for other ages must be gathered and the NART-Raven difference in disease (especially dementia) must

be explored. The results presented in this thesis, the similarity of NART in dementia and in healthy groups suggest that this 'instantaneous' approach may well be valid in people with dementia. Clearly this must be studied further, but is suggestive of a future clinical application.

Why does the NART – a test of the reading aloud of 50 words – hold in dementia? Possible mechanisms underlying this were discussed above. Functional neuroimaging (with the task being NART testing and other verbal tests) of healthy elderly subjects could be compared to people with dementia. This would answer some questions about regional brain activation during the NART. This would present a useful opportunity to test the cognitive reserve hypotheses: people with differing mental ability in childhood may recruit different brain regions in response to cognitive stress (in this case, the NART). This study could also contain testing of semantic memory to further elucidate mechanisms.

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Appendix: Papers published from work in this thesis

CME Pronunciation of irregular words is preserved in dementia, validating premorbid IQ estimation

B. McGurn, MB, ChB; J.M. Starr, FRCPEd; J.A. Topfer, BA, MSc; A. Pattie, BSc; M.C. Whiteman, PhD; H.A. Lemmon, MA; L.J. Whalley, MD; and I.J. Deary, PhD

Abstract—The National Adult Reading Test (NART), used to estimate premorbid mental ability, involves pronunciation of irregular words. The authors demonstrate that, after controlling for age 11 IQ test scores, mean NART scores do not differ in people with and without dementia. The correlation between age 11 IQ and NART scores at about age 80 was similar in the groups with ($r = 0.63$, $p < 0.001$) and without ($r = 0.60$, $p < 0.001$) dementia. These findings validate the NART as an estimator of premorbid ability in mild to moderate dementia.

NEUROLOGY 2004;62:1184–1186

The diagnosis of dementia depends on demonstrating cognitive decline from a prior level.[1] Ideally, this would be measured by comparing current cognitive status with observed premorbid cognitive function. However, measures of previous mental ability are rarely available, leading to reliance upon an estimate of premorbid mental ability in both clinical practice and research. Such an estimate is provided by the National Adult Reading Test[2] (NART), which assesses pronunciation of 50 English words that do not follow regular grapheme-phoneme and stress rules. Examples of irregular words include ache (compared with the regular word cake) and thyme (compared with the identically pronounced regular word time). The NART is a valuable clinical tool. However, recent debate has cast doubt as to whether performance on the NART is impervious to cognitive decline.[3-7] The present study addresses the following two unanswered questions concerning the NART: Does mild to moderate dementia reduce NART scores? Do both nondemented and demented subjects show the same association (regression slope) between mental ability in youth and NART scores in old age?

Methods. On June 1, 1932, almost all children at school in Scotland born in 1921 (n = 87,498) participated in the Scottish Mental Survey 1932 (SMS1932).[8] This involved measurement of psychometric intelligence using a version of the Moray House Test No. 12 (MHT). We examined the relationship between NART score at about age 80 years and childhood ability in two groups of people who took part in the SMS1932: one group who developed dementia in old age and another group who did not.

For all patients, the diagnosis of dementia was made at clinical interview, applying International Classification of Diseases (ICD-10) criteria, taking into account detailed neuropsychological testing. Patients were identified in two follow-up studies of SMS1932 currently underway in Scotland. First, there were 97 patients born in 1921 assessed at the Lothian Memory Treatment Center (LMTC) up to December 2002. Of these, 29 had a NART measure and were matched to their MHT score at age 11. Second, the Aberdeen Birth Cohort 1921 (ABC1921) recruited 235 former participants in the SMS1932, performing clinical examination and neuropsychological assessment. Of these, 16 participants met ICD criteria for dementia either on recruitment or during follow-up (annually from 1998). For the ABC1921 members, NART and contemporaneous Mini-Mental State Examination[9] (MMSE) were taken from the time closest to the date of diagnosis of dementia. The diagnosis of dementia was probable Alzheimer disease (AD) in 57.8% of patients, unspecified dementia in 33.3%, vascular dementia in 6.7%, and possible AD in 2.2%.

The group without dementia comprised members of the Lothian Birth Cohort 1921. This study followed up, between 1999 and 2001, 550 surviving participants of the SMS1932 residing in the Edinburgh area. All lived independently in the community. After excluding those who had a clinical history of dementia (n = 5) or an MMSE of ≤ 24 (n = 21), 466 had MHT scores recorded at age 11. Of these, 464 had a NART performed.

See also page 1038

From the Departments of Geriatric Medicine (Drs. McGurn and Starr) and Psychology (Drs. McGurn, Whiteman, and Deary, and A. Pattie), University of Edinburgh; Lothian Memory Treatment Centre (J.A. Topfer), Edinburgh; and Department of Mental Health (Dr. Whalley, H.A. Lemmon), University of Aberdeen, UK.

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Address correspondence and reprint requests to Professor I.J. Deary, Department of Psychology, University of Edinburgh, 7 George Square, Edinburgh EH8 9JZ, UK; e-mail: I.Deary@ed.ac.uk

Table *Differences in age, MMSE, NART, and MHT in people with and without dementia*

Age and tests	No dementia, n = 464	Dementia, n = 45	*p* Value
Age at NART testing, y	79.1 (0.6)	79.0 (1.5)	0.51
MMSE	28.4 (1.3)	22.3 (4.2)	<0.001
MHT	47.0 (11.5)	38.0 (14.2)	<0.001
NART	34.5 (8.0)	28.2 (9.8)	<0.001

Values are mean (SD).

MMSE = Mini-Mental State Examination; NART = National Adult Reading Test; MHT = Moray House Test No. 12.

Results. There was no difference in age at NART testing between the dementia and nondementia subjects ($t = -0.66$, $p = 0.51$) (table). They differed on MMSE scores (Cohen $d = 1.91$, $p < 0.001$) (see the table). The nondementia group scored at or close to maximum of 30. Most in the dementia group scored in the mild-moderate dementia range: 64% had a score ≤ 24. When the MMSE scores were adjusted for MHT scores at age 11, the groups still differed on MMSE ($d = 1.76$, $p < 0.001$).

The dementia group scored significantly lower on the NART, but also scored lower on the MHT at age 11 (see the table). Mean MHT score of the dementia group (38.0) is higher than the population mean (34.5),[8] and the mean MHT of the nondementia group (47.0) indicates they were relatively able as children. NART scores were adjusted by linear regression for MHT scores at age 11. Before adjustment of NART for MHT scores, the effect of dementia versus nondementia group on NART scores was significant ($d = 0.67$, $p < 0.001$). After adjustment for MHT scores the dementia and nondementia groups no longer differed on NART scores ($p = 0.12$), and the effect size was markedly reduced ($d = 0.27$).

Next, we addressed the association between NART and childhood mental ability in the dementia and nondementia groups. The scattergrams and regression lines describing the association between NART and MHT are similar in the dementia and nondementia groups (figure). Pearson correlations between NART and MHT were similar in the dementia group ($r = 0.63$) and the nondementia group ($r = 0.60$). These correlations do not differ ($z = 0.239$, $p = 0.81$). Regression slopes were compared and did not differ ($t = 0.273$, $df = 505$, $p = 0.79$).

Might the comparable correlations between the NART and MHT be due to undiagnosed or incipient dementia in the nondementia group? To assess this, the highest MMSE scorers in the nondementia group and the lowest scorers in the dementia group were examined. When the nondementia group was restricted to those with MMSE scores of 29 or 30 (usually taken as cognitively normal), the NART-MHT correlation was 0.63 ($n = 243$, $p < 0.001$). When the dementia group was restricted to those with MMSE scores less than 21 (usually taken as important impairment), the NART-MHT correlation was 0.71 ($n = 14$, $p = 0.005$). Again, these correlations do not differ ($z = 0.445$, $p = 0.66$).

There is a correlation between NART and MMSE in the nondementia group ($r = 0.40$, $p < 0.001$) and in the group with dementia ($r = 0.51$, $p < 0.001$) but there is no difference between these correlations ($z = 0.867$, $p = 0.39$).

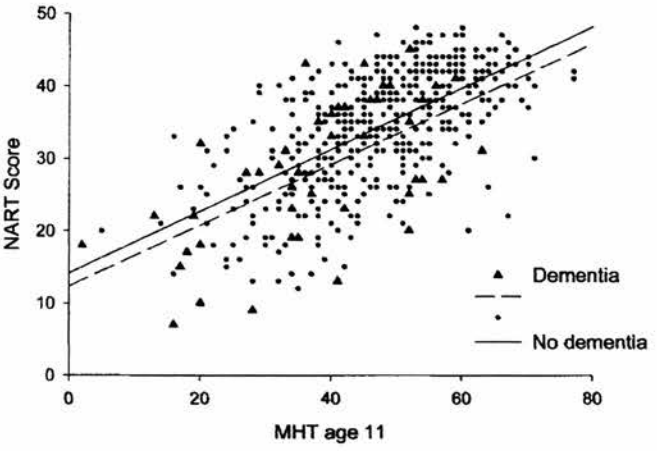

Figure. Scattergram with fitted regression lines of National Adult Reading Test (NART) and Moray House Test No. 12 (MHT) in people with and without dementia.

Discussion. This study compared NART scores in people with and without dementia after controlling for actual premorbid ability test scores recorded in youth. Those with dementia scored lower on NART and had lower childhood mental ability scores, consistent with lower childhood IQ predisposing to late-onset dementia.[10] After controlling for childhood mental ability, there was no difference in NART scores between the groups. A similar adjustment for childhood ability scores did not diminish the MMSE score differences between the two groups. Additionally, the correlation between NART scores and childhood ability test scores was very similar in the groups. Thus, in this sample, the NART has passed a robust assessment of its validity as an estimate of premorbid ability.

Our results show a constant relationship between NART and childhood ability in the context of very different levels of current cognitive status, conflicting with the suggestion that NART performance might be sensitive to degree of cognitive impairment.[3-6] It may be, however, that the ability to pronounce words holds generally in dementia, declining precipitously beyond a certain cut-off point. Possibly, if we had looked at more severe dementia, the relationship between NART score and MHT would not have held.

If the value of the NART in estimating premorbid intelligence was attenuated in the presence of dementia, then it would be expected that the correlation between NART and MMSE would be different in our two groups. This was not the case.

The ability to read aloud, which relies on retrieval of words from a mental lexicon utilizing semantic memory, declines as dementia progresses and retrieval breaks down.[4] Our results suggest that where there is greater childhood mental ability, the aspects of semantic memory involved in pronunciation remain relatively intact. Alternatively, they could be

taken to mean that semantic memory is less important in the pronunciation of irregular words than has previously been thought, pointing the way to separate, but as yet unidentified, neural mechanisms.

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Life long changes in cognitive ability are associated with prescribed medications in old age

John M. Starr[1]*, Brian McGurn[1,2], Martha Whiteman[2], Alison Pattie[2], Lawrence J. Whalley[3] and Ian J. Deary[2]

[1]*Geriatric Medicine Unit, University of Edinburgh, Edinburgh, UK*
[2]*Department of Psychology, University of Edinburgh, Edinburgh, UK*
[3]*Department of Mental Health, University of Aberdeen, Edinburgh, UK*

SUMMARY

Objectives To determine the association between prescribed medication and life long changes in cognitive ability.
Design Retrospective cohort study.
Setting Community residents of a largely urban region of South East Scotland.
Participants Four hundred and seventy-eight survivors of the 1932 Scottish Mental Health Survey ($n = 87\,498$) without dementia.
Measurements The Moray House Test (MHT) of intelligence administered at age 11 and age 80 years. Hospital Anxiety and Depression Scale (HADS) score, history of disease and current prescribed medications age 80 years.
Results After adjusting for sex, neuroactive drugs had a detrimental effect on life long cognitive change age ($F = 12.2$, $p = 0.001$, partial eta-squared $= 0.026$), statins a beneficial effect ($F = 5.78$, $p = 0.017$, partial eta-squared $= 0.013$) and polypharmacy a detrimental effect ($F = 6.46$, $p = 0.011$, partial eta-squared $= 0.014$). In the optimal model estimated marginal means revealed: a relative improvement for statin users, IQ age 11 = 93.2 (95% CI 87.9–98.4) and age 80 = 100.6 (95% CI 95.3–105.9); compared with non-users, IQ age 11 = 100.9 (95% CI 99.4–102.3) and age 80 = 100.0 (95% CI 98.6–101.5).
Conclusions Clinically, the degree to which drugs impair cognition in relatively fit, older people may not be apparent. However, in population terms, medication use, particularly polypharmacy, is important. Statins, used as currently indicated for cardiovascular disease, appear promising in ameliorating cognitive decline in older people. However, firm recommendation of their use should await the outcome of ongoing randomised clinical trials. Copyright © 2004 John Wiley & Sons, Ltd.

KEY WORDS — cognition; older people; drugs; 3-hydroxy-3-methyglutaryl coenzyme A reductase inhibitors

INTRODUCTION

Drugs are a common cause of delirium in older people (Johnson *et al.*, 1990; Inouye *et al.*, 1993). Some drugs may induce dementia by acting on neurotransmitters or neurotrophic factors (Starr and Whalley, 1994a). The cerebral reserve hypothesis (Kay *et al.*, 1964) would allow drugs to produce minor neuropsychological decrements in the majority of people taking them, but these decrements only to be clinically apparent in those close to some critical threshold (Foy and Starr, 2000). Pre-morbid mental ability would be an important determinant of such cerebral reserve (Starr *et al.*, 1992). Alternatively, drugs may have little effect on mental abilities in the majority of older people and only lead to cognitive decline in a vulnerable group (Larson *et al.*, 1987), but not healthy individuals (Starr *et al.*, 1997). In a review of cognitive side effects of medications (Meador, 1998), Meador concluded that 'a great deal of individual variability in tolerance may be seen across patients', that polypharmacy was associated with increased risk, but that much was unknown about this problem.

*Correspondence to: Dr J. M. Starr, Geriatric Medicine Unit, University of Edinburgh, Royal Victoria Hospital, Craigleith Road, Edinburgh, EH4 2DN UK. E-mail: john.starr@ed.ac.uk

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In his review, Meador parsimoniously divided candidate drugs into neuroactive and 'medicinal', though this division is somewhat arbitary because 'medicinal' drugs may exert their effects on cognition via central mechanisms. Cardiovascular agents, mainly antihypertensives and statins, dominated the 'medicinal' category. Elevated blood pressure, itself, is associated with cognitive impairment (Starr, 1999) and antihypertensive therapy reduces the risk of dementia (Forette *et al.*, 1998). However, calcium channel antagonists and loop diuretics have been associated with lower cognitive test scores than β-blockers and thiazides (Heckbert *et al.*, 1997). Other antihypertensive classes, such as angiotensin-converting enzyme (ACE) inhibitors either have a neutral (Bulpitt and Fletcher, 1992) or potentially beneficial (Starr and Whalley, 1994b) effect on cognition. Determining whether antihypertensive agents contribute to cognitive decline to any major degree in a naturalistic setting would further inform clinicians about any potential risks in everyday practice.

Some drugs may have a beneficial rather than adverse effect on cognition in older people. Hypercholesterolaemia is linked to increased β-amyloid deposition in a transgenic mouse model of Alzheimer's disease (Refolo *et al.*, 2001), and to the later development of mild cognitive impairment (Kivipelto *et al.*, 2000) and Alzheimer's disease (Jarvik *et al.*, 2000) in humans. Lowering cholesterol with statins is associated with reduced dementia prevalence and improved cognition in some studies (Hajjar *et al.*, 2002; Yaffe *et al.*, 2002), but not others (Muldoon *et al.*, 2000; Gibellato *et al.*, 2001). Other agents thought to ameliorate cognitive decline are aspirin (Meyer *et al.*, 1989) and non-steroidal anti-inflammatory agents (NSAIDS) (Rozzini *et al.*, 1996).

Approximately half of the variance in IQ scores in old age is explained by childhood IQ (Deary *et al.*, 2000); sex and Apolipoprotein E explain a further small proportion of individual differences (Deary *et al.*, 2001). Thus, allowing for error variance, it is likely that around 40% of variance in IQ scores in old age is determined by 'extrinsic' factors. Both disease and medication use are commoner in older than younger adults and are possible 'extrinsic' factors. However, it is unclear to what extent disease and drugs contribute to this variance. Knowledge of IQ before disease onset is essential in untangling possible causal directions because lower childhood IQ is itself related to greater risk of disease and premature mortality (Whalley and Deary, 2001). Lower cognitive test scores in old people with disease may just reflect their life-long mental ability. Previously, we investigated the effects of medication on cognitive change in 603 people born in Edinburgh between 1906–1920 who were disease free and on no drug treatment at baseline (Starr *et al.*, 1997). We found no significant difference between those who had started medication and those who remained drug free on the Mini-Mental State Examination (MMSE) (Folstein *et al.*, 1975) after four years of follow-up. However, the MMSE has limited variance in healthy populations and we may therefore have missed subtle effects. Such relatively insensitive cognitive outcome measures have been used in other studies of the influence of 'extrinsic' factors on cognition (Ford *et al.*, 1996; Cattin *et al.*, 1997; Cacciatore *et al.*, 1998). We investigated the association of disease and medication use in a sample from a unique national population of older people with known childhood IQ's using the same sensitive, validated cognitive measure nearly seventy years later.

METHOD

The Scottish Mental Survey of 1932 (SMS1932) tested mental ability in people born in 1921 ($n = 87\,498$). The SMS1932's Moray House Test (MHT) was validated against the Stanford Binet test and includes verbal reasoning, numerical, spatial and other items (Scottish Council for Research in Education, 1933). From 1999–2001 we traced and retested 550 people from Edinburgh who were born in 1921 (the Lothian Birth Cohort 1921). The study was conducted with permission from the local research ethics committee. All participants gave written informed consent and were living independently. As previously described (Deary *et al.*, 2002), we excluded people with a history of dementia or with a MMSE (Folstein *et al.*, 1975) of less than 24. We traced their scores on the MHT from SMS1932; re-administered the MHT using the same instructions and time limit as the SMS1932. We also administered the Hospital Anxiety and Depression Scale (HADS) (Zigmond and Snaith, 1983), and collected information on years of full-time education, social class, whether the participant lived alone and smoking habit.

We enquired about history of any disease and categorised these, using criteria previously established for related cohorts (Starr *et al.*, 1997, 2000a), into cardiac, cerebrovascular, non-cardiac and non-cerebrovascular vascular disease (e.g. peripheral arterial disease, abdominal aortic aneurysm etc), hypertension, diabetes, thyroid disorder, neoplasia and other disease. We categorised regular drugs taken according to *ad hoc* hypotheses suggested by Meador's review into

neuroactive (e.g. major and minor tranquilisers, antidepressants, antiepileptics etc), β-blockers, ACE inhibitors, statins, aspirin and NSAIDs, any cardiovascular medication and any other medication.

Following data checking, analyses were performed using SPSS 11.0 statistical software package. MHT scores were converted to IQ scores corrected for exact age in days as previously described (Deary *et al.*, 2000). General linear modelling was performed using a repeated measures design for IQ at age 11 and 80 years. Full factorial models were specified to adjust for potential interactions between independent variables. Effect sizes, as an estimate of the proportion of variance in the dependent variable explained by an independent variable, were expressed as partial eta-squared; the proportion of variance explained by the model equates to the sum of all the partial eta-squareds. Of note is that conversion of absolute MHT scores to IQ scores meant that the analyses addressed relative rather than absolute cognitive change. Also in these repeated measures models, the partial eta-squared relates to only that variance unexplained by 'stable' life-long mental ability.

RESULTS

Four hundred and seventy-eight participants had MHT scores at ages 11 and 80 years and were not demented. MHT-derived IQ was standardised at each age; mean absolute scores were higher age 80. Men ($n = 199$) had a mean IQ of 99.6 (SD 15.7) age 11 and 101.1 (SD 14.8) age 80. Women ($n = 279$) had a mean IQ of 100.5 (SD 14.2) age 11 and 98.7 (SD 14.9) age 80]. As previously reported, there was a significant effect of sex on change in IQ score between age 11 and 80 ($F = 8.39$, $p = 0.004$) (Deary *et al.*, 2001). The sample contained relatively few participants from social class 4 or 5 (social class 1 $n = 101$, social class 2 $n = 174$, social class 3 $n = 180$, social class 4 $n = 12$, social class 5 $n = 8$); no effect of social class on change in IQ score between age 11 and 80 was detected ($F = 0.85$, $p = 0.51$). IQ scores for specific disease categories are presented in Table 1. The only significant effect uncorrected for any covariates was a relative improvement for participants with non-cardiac and non-cerebrovascular vascular disease ($F = 4.18$, $p = 0.016$). This effect remained significant after adjusting for sex ($F = 3.53$, $p = 0.030$, partial eta-squared = 0.015). IQ scores for specific classes of drug are presented in Table 2. The only significant effect uncorrected for any covariates was a relative deterioration over time for participants taking neuroactive drugs ($F = 19.0$, $p < 0.001$). This effect remained significant after adjusting for sex ($F = 12.2$, $p = 0.001$, partial eta-squared = 0.026), and the effects of statins also became statistically significant after adjusting for sex ($F = 5.78$, $p = 0.017$, partial eta-squared = 0.013), with those on statins showing a relative improvement in IQ. The total number of drugs taken was also significant after adjusting

Table 1. Standardised IQ scores age 11 and 80 years in the Lothian 1932 Scottish Mental Survey cohort according to presence (definite [def] or uncertain [uncrtn]) or absence of disease

Disease category	N with disease	Mean IQ (SD) age 11 years		Mean IQ (SD) age 80 years	
		Disease	No disease	Disease	No disease
Cardiac	82 def, 63 uncrtn	99.1 (17.0) 98.3 (13.6)	100.7 (14.5)	98.7 (16.3) 98.7 (14.3)	100.0 (14.7)
Cerebrovascular	37 def, 3 uncrtn	100.0 (12.8) 103.8 (19.5)	100.1 (15.0)	97.3 (19.9) 106.8 (17.2)	99.9 (14.6)
Non-cardiac, non-cerebrovascular vascular*	38 def, 2 uncrtn	98.9 (13.3) 105.7 (7.3)	100.3 (15.0)	100.8 (14.3) 82.5 (12.5)	99.7 (15.0)
Hypertension	198 def, 4 uncrtn	100.0 (13.3) 102.4 (28.3)	100.3 (15.7)	100.0 (14.3) 93.9 (25.2)	99.6 (15.3)
Diabetes	22 def	102.1 (10.7)	100.1 (15.0)	97.2 (19.5)	99.8 (14.7)
Thyroid	62 def	100.7 (15.5)	100.1 (14.8)	100.3 (13.9)	99.6 (15.1)
Neoplasia	30 def, 14 uncrtn	103.5 (14.0) 96.2 (17.0)	100.1 (14.8)	99.2 (13.5) 95.5 (11.9)	99.9 (15.1)
Other disease	50 def	99.5 (14.7)	100.3 (15.0)	95.9 (17.4)	100.1 (14.6)

*Significant categories at $p < 0.05$.

Table 2. Standardised IQ scores age 11 and 80 years in the Lothian 1932 Scottish Mental Survey cohort according to medication use

Drug class	N on drug	Mean IQ (SD) age 11 years		Mean IQ (SD) age 80 years	
		Drug	No drug	Drug	No drug
Aspirin	145	100.8 (14.0)	100.2 (14.9)	100.4 (14.9)	99.7 (14.6)
NSAID	46	102.6 (13.5)	100.1 (14.7)	101.1 (13.0)	99.8 (14.9)
β-blocker	82	102.6 (14.0)	99.9 (14.7)	101.4 (14.3)	99.6 (14.8)
ACE inhibitor	75	99.2 (16.0)	100.6 (14.3)	97.8 (17.3)	100.3 (14.1)
Statin	37	96.8 (15.1)	100.7 (14.5)	99.8 (12.4)	99.9 (14.9)
Any cardiovascular agent	262	100.6 (14.2)	100.1 (15.1)	99.9 (15.1)	99.9 (14.2)
Any neuroactive agent*	32	104.6 (14.0)	100.1 (14.6)	95.2 (14.2)	100.2 (14.7)

*Significant categories at $p < 0.05$.

for sex ($F = 6.46$, $p = 0.011$, partial eta-squared = 0.014), with participants on more drugs showing a worsening of IQ at age 80 relative to age 11.

The effects of non-cardiac and non-cerebrovascular disease, neuroactive drugs, statins and the total number of drugs taken all remained significant after adjusting for years of full-time education, social class, living alone, smoking habit and HADS anxiety and depression scores. Entering the four significant variables into a repeated measures, general linear model including sex, a history of non-cardiac and non-cerebrovascular disease ($F = 1.87$, $p = 0.16$) and neuroactive drugs ($F = 1.21$, $p = 0.27$, partial eta-squared = 0.022) were no longer significant. The optimal model comprised sex ($F = 10.5$, $p = 0.001$), total number of drugs ($F = 13.0$, $p < 0.001$, partial eta-squared = 0.028) and statin use ($F = 13.0$, $p < 0.001$, partial eta-squared = 0.028). Estimated marginal means revealed: a relative improvement for men, IQ age 11 = 93.4 [95% Confidence Intervals (CI) 89.2–97.6] and age 80 = 100.1 (95% CI 95.9–104.4), compared with women, IQ age 11 = 100.6 (95% CI 97.5–103.8) and age 80 = 100.5 (95% CI 97.3–103.7); for statin users, IQ age 11 = 93.2 (95% CI 87.9–98.4) and age 80 = 100.6 (95% CI 95.3–105.9), compared with non-users, IQ age 11 = 100.9 (95% CI 99.4–102.3) and age 80 = 100.0 (95% CI 98.6–101.5). Greater number of drugs taken was associated with a relatively lower IQ score age 80 compared with age 11.

DISCUSSION

In this sample, medication use was associated with a small, but significant effect on IQ change from childhood to old age. A greater number of medications used was associated with a relative worsening of IQ, explaining about 2.2% of the variance in change over time, whilst statin use was associated with a relative improvement, explaining about 2.8% of variance. Other medication classes mostly had more subjects than that of statins and neuroactive drugs, suggesting that if they had an effect in this sample it is likely that it is fairly small. Relative improvement in cognition with statins is consistent with those studies that looked at their effects in older people over prolonged periods (Hajjar *et al.*, 2002; Yatte *et al.*, 2002) rather than younger adults over shorter periods (Muldoon *et al.*, 2000; Gibellato *et al.*, 2001). Moreover, this sample of people without dementia manifested relative improvement in cognition at the age of 80 years, a cut-off age for benefit of statins in preventing Alzheimer's disease in the Canadian Study of Health and Aging (Rockwood *et al.*, 2002). Others report statins reducing Alzheimer's disease risk (Jick *et al.*, 2000; Wolozin *et al.*, 2000): statins may ameliorate adverse changes within the brain associated with cholesterol metabolism that render it vulnerable to Alzheimer's disease (Naidu *et al.*, 2002). Statin users had lower childhood IQ's, as might be expected, but had caught up relatively by age 80.

Although non-cardiac and non-cerebrovascular vascular disease was associated with a significant effect on IQ change, this disappeared once other variables were adjusted for. No other disease category had a significant association, but numbers in some disease categories were smaller than in drug classes, thus sizeable effects may have been missed. Moreover, the spectrum of severity of disease is likely to be biased towards minor, stable illness since the participants were fit enough to attend for a fairly lengthy assessment. Presence or absence of disease is probably a very imprecise measure of health status in old age (Starr *et al.*, 2000a). The total number of drugs taken may be a better indicator of disease burden, and it is unclear whether it is the drugs themselves or the underlying disease for which they are prescribed that is causing the relative decline in IQ. Within this, however, some drugs, and in particular statins, may

exert a beneficial effect, perhaps ameliorating effects of disease.

Other studies also found that the effect size of many diseases on mental ability to be generally quite small. Hypertension accounts for only a small proportion of the variance in mental ability in old age (Starr, 1999) and differentially impairs fluid intelligence compared with memory (Deary *et al.*, 1998). By contrast, Type 2 Diabetes mellitus predominantly affects domains of memory (Strachan *et al.*, 1997), thus its effects are less likely to be seen with a general intelligence test such as the MHT. Stroke, for which both hypertension and diabetes are important risk factors, is associated with more marked impairment of fluid intelligence (Starr *et al.*, 2000b) but this sample is likely to be biased towards those with more minor disability after stroke and hence with less cognitive decline.

Although medications had only a small effect on change in IQ over the lifetime, sample bias may have underestimated this. Drugs may have had a greater impact on potential participants who were sicker, and thus on more medications, who would be less likely to attend for assessment. Our sample contained people who were cognitively normal or who had only minor degrees of cognitive impairment (Deary *et al.*, 2001) so family doctors are unlikely to have limited medication use in those who they thought might be more unreliable taking tablets because of reduced mental ability. Trials, such as that ongoing for pravastatin (Houx *et al.*, 2002) provide the best evidence of cognitive change associated with drugs, but these cannot easily take into account the effects of polypharmacy. It may be due to interactions between different classes of drug that cognitive side effects most commonly occur, and clinical trials are unlikely to be powered to detect such sub-group effects. Polypharmacy was specifically identified by Meador's review as an important risk factor for cognitive side effects in old age (Meador, 1998). Older neuroactive agents were also singled out by Meador, but the prescription of newer atypical psychotics and antidepressants in our sample may explain why their effects on cognition disappeared once other factors were controlled for. Heterogeneity of agents within other classes of drug (e.g. more and less cardio-selective β-blockers) may also have masked effects of older drugs on cognition.

We conclude that if non-demented, older people are fit enough to attend for relatively lengthy assessments, disease makes a minimal contribution to their mental ability test scores, but that despite this medication, in particular polypharmacy, does have a significant, though probably not clinically detectable, effect. In population terms, this small effect of medication use, particularly polypharmacy, is important. In terms of public health policy aimed at preventing cognitive decline in old age, it may be more important to target people on multiple medications and reduce these rather than focus on specific classes of drug. Statins, used as currently indicated for cardiovascular disease, appear promising in preventing cognitive decline in older people. However, firm recommendation of their use should await the outcome of ongoing randomised clinical trials.

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